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The Genetic Resource

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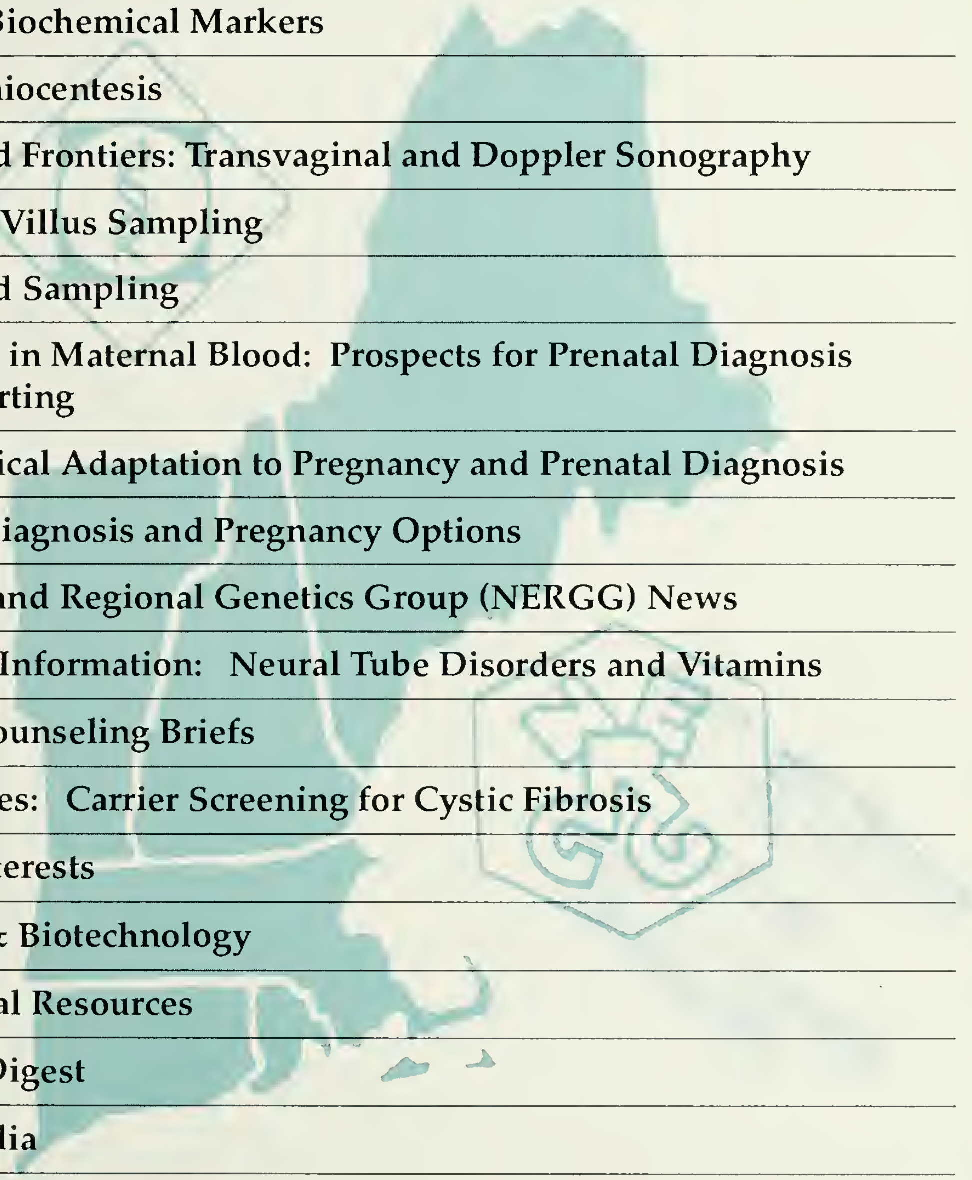

A Note from The Editors
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Early Amniocentesis
Ultrasound Frontiers: Transvaginal and Doppler Sonography
Chorionic Villus Sampling
Fetal Blood Sampling
Fetal Cells in Maternal Blood: Prospects for Prenatal Diagnosis by Cell Sorting
Psychological Adaptation to Pregnancy and Prenatal Diagnosis
Prenatal Diagnosis and Pregnancy Options
New England Regional Genetics Group (NERGG) News
Teratogen Information: Neural Tube Disorders and Vitamins
Genetic Counseling Briefs
Legal Notes: Carrier Screening for Cystic Fibrosis
Citizen Interests
Genetics & Biotechnology
Educational Resources
Genetics Digest
In the Media
Past Issues
Genetic Counseling Centers in New England

1991
Volume 6, Number 1

1ST NEW ENGLAND REGIONAL ISSUE

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The Genetic Resource

1991 Vol. 6, No.1

1st New England Regional Issue

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4 A NOTE FROM THE EDITORS

Robin J.R. Blatt, M.P.H.
Wayne A. Miller, M.D.
Paula K. Haddow, M.A.T.

FEATURES

5 **Enhanced Prenatal Screening for Down Syndrome Using Multiple Biochemical Markers**
by Jacob A. Canick, Ph.D., Gail Barsel Bowers, M.S.

10 **Early Amniocentesis**
by Wayne A. Miller, M.D., Barbara Thayer, M.S.

12 **Ultrasound Frontiers: Transvaginal and Doppler Sonography**
by Karen M. Ferroni, M.D., Avis Vincensi, R.T., R.D., M.S.

15 **Chorionic Villus Sampling**
by Miriam Schoenfeld DiMaio, M.S.W., Maurice Mahoney, M.D.,

18 **Fetal Blood Sampling**
by Mary D'Alton, M.D.

24 **Fetal Cells in Maternal Blood: Prospects for Prenatal Diagnosis by Cell Sorting**
by Diana W. Bianchi, M.D.

28 **Psychological Adaptation to Pregnancy and Prenatal Diagnosis**
by Solveig Pflueger, M.D.

31 **Prenatal Diagnosis and Pregnancy Options**

Continuing the Pregnancy
by Marsha Saxton, Betsy Anderson, Robin J.R. Blatt

Special Needs Adoption
by Joanne Finnegan

Termination Support Groups
by Barbara Thayer, M.S., Leslie Ciarleglio, M.S., Jodi Rucquoi, M.S.

IN EVERY ISSUE

43 **New England Regional Genetics Group (NERGG) News**

59 **Teratogen Information**

62 **Genetic Counseling Briefs**

65 **Legal Notes**

69 **Citizen Interests**

71 **Genetics & Biotechnology**

72 **Educational Resources**

73 **Genetics Digest**

99 **In the Media**

100 **Past Issues**

102 **Genetic Counseling Centers in New England**

General Information

The Genetic Resource is published semiannually. It has been established to share current information on new research, developments, trends and ideas in the field of genetics. Founded in 1983 , **The Genetic Resource** now has a circulation of approximately 7,500 readers. **The Genetic Resource** is currently distributed to obstetricians, pediatricians, family practitioners, internists, geneticists, genetic counselors, nurses, social workers, public health planners and health policy makers, industry representatives, legislators, consumers and other individuals and organizations interested in human genetics.

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The editors reserve the right to edit all material on the basis of space and relevancy. We welcome the submission of articles, commentaries, or questions on subjects relative to human genetics.

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THE GENETIC RESOURCE

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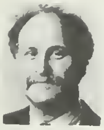

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A Note from The Editors

This 11th issue of **The Genetic Resource** may look and feel different from past issues to you. It represents the 1st New England Regional Issue, assembled with the assistance of a newly formed group of Editorial Advisors that representing each of the six New England states. Format, size, content and scope have changed. In addition, we are pleased to announce that Paula K. Haddow, Director of Education Services at the Foundation for Blood Research in Scarborough, Maine, has joined us as a Co-Editor to help launch this as a regional publication.

The expansion of content and distribution of **The Genetic Resource** is a reflection of the increasing importance of medical genetics in health care. In 1983 we launched this publication with the conviction that a resource was needed to concisely present up to date scientific developments in human genetics and to help practitioners assess the human impact of these developments in clinical practice. What began as an 18 page newsletter with limited distribution to professionals has become a 64 page journal with a circulation of more than 7,500 that now includes consumer organizations and interested individuals. A review of the titles covered in the 10 issues published over the past eight years is a litany of the major developments and controversies in medical genetics over the past decade. The features in this current issue focuses on topics in prenatal genetic diagnosis, a subject that has recurrently appeared as new techniques and applications have emerged.

One of the few certainties about the future is that there will continue to be new developments in health care as the result of research in genetics and the international focus on the Human Genome Initiative. **The Genetic Resource** will aim to bring you timely information about new research findings, plans for technology transfer and suggested guidelines for clinical practice. In addition, we hope this publication will serve as a local forum for discussion and debate of the accompanying ethical, legal and social issues that relate to genetic medicine.

Our pledge for the future is simple: We will continue to try to improve **The Genetic Resource.** We look to you, our readers, to help us shape this publication into one that you feel is most practical and helpful. We welcome your comments and would like to hear from you.

Robin J.R. Blatt

Wayne A. Miller

Paula K. Haddow

Enhanced Prenatal Screening for Down SyndromeUsing Multiple Biochemical Markers

-Jacob A. Canick, Ph.D., Gail Barsel Bowers, M.S.

In recent months, a new biochemical screening test has been introduced by both nonprofit and commercial genetics programs. Using a variety of proprietary names such as "Fetoscreen," "Triple Screen," "AFP3," and "Trisomy Screening Profile," (we and others use the name "AFP PLUS"), these programs claim significant enhancement in prenatal screening for pregnancies affected by fetal Down syndrome. A few programs claim enhancement in screening for other aneuploidies as well. Are the claims justified? In this article, we will describe the evolution of the new test and the published evidence that supports and refutes the claims that have been made. In addition, we will describe the screening protocol and discuss issues of particular clinical importance.

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Background

Maternal age as a prenatal screening test for Down syndrome.

The most commonly used method to determine if a pregnancy is at high risk for fetal Down syndrome is to apply the association between advanced maternal age and increased risk. Beginning at age 35, when the second trimester risk is about 1 in 270, pregnant women in this country are considered to be at sufficient risk to be offered amniocentesis for karyotype analysis. As a group, these patients comprise from 5 to 7% of the entire pregnant population in New England and will give birth to between 20 and 30% of all babies affected with Down syndrome. It is increasingly common for physicians to routinely offer genetic amniocentesis to women who are 33 and 34, thus increasing the rate of amniocentesis to 10% of the pregnant population.

MSAFP as a prenatal screening test for Down syndrome.

In 1984, Merkatz *et al.* reported that alpha-fetoprotein (AFP) was lower than normal in second trimester maternal serum (MS) samples from pregnancies affected by Down syndrome and trisomy 18.[1] Cuckle *et al.* confirmed the association between low MSAFP and Down syndrome pregnancy, reported that MSAFP and maternal age were independent screening markers, and proposed a screening test that would incorporate these findings.[2] Within one year, laboratories were using the new screening method that, for the first time, could expand the identification of high risk pregnancies to women under the age of 35. Today, the majority of prenatal AFP screening programs in the United States provide risk estimates for Down syndrome pregnancy based on MSAFP and maternal age in combination. The result is that low MSAFP screening, applied to the younger pregnant population, will result in the selection of 3 to 4% of those patients as candidates for amniocentesis and will allow detection of about 20% of the cases of fetal Down syndrome in the younger pregnant population as shown in the results of the recent New England Regional Genetics Group collaborative study.[3] Therefore, the combination of MSAFP and maternal age as a screening method in younger women and age alone as the screening method in older women will result in a potential Down syndrome detection rate of 40 to 50%. This approach, however, will require amniocentesis on 8 to 12% of the entire pregnant population.

New Markers In Prenatal Screening For Down Syndrome

Unconjugated estriol

With the discovery that pregnancies affected with fetal Down syndrome are associated with lower levels of MSAFP, we postulated that the levels of other biochemical markers of fetoplacental origin might also be abnormal in Down syndrome pregnancy. AFP is made primarily in the fetal liver during the second trimester of pregnancy. Indirect data indicated that the livers of fetuses affected with Down syndrome might be producing less than average amounts of AFP.[4] The fetal liver also participates in the biosynthesis of the fetoplacental steroid hormone, estriol (uE3). Therefore, MSuE3 might also be lower than normal in pregnancies affected with fetal Down

Summary of Key Points

- *Today, the majority of prenatal AFP screening programs in the United States provide risk estimates for Down syndrome pregnancy based on MSAFP and maternal age in combination.*
- *MSuE3 is about 25 to 30% lower in Down syndrome pregnancy and the measurement of MSuE3 along with MSAFP substantially enhances screening sensitivity.*
- *Bogart et al. demonstrated that matemal serum levels of the placental hormone, human chorionic gonadotropin (hCG), were also abnormal in pregnancies affected with fetal Down syndrome. The surprising finding was that MShCG levels were higher than normal.*
- *If a second trimester risk cut-off of 1 in 270 is selected, the initial positive rate is predicted to be 7.2% with a detection rate of 67%. If these predicted results hold true, the use of the three markers in combination will substantially enhance screening specificity and sensitivity over the currently used method of age alone for older women and age plus MSAFP for younger women.*
- *If the inclusion of MSuE3 results in a 30% reduction in the amniocentesis rate, then the use of MSuE3 would be cost effective.*
- *With enhanced screening, maternal age becomes just one of four determinants of risk for fetal Down syndrome.*
- *Because MShCG levels are low rather than high in fetal trisomy 18, these pregnancies would most likely not be identified by a screening protocol designed to detect Down syndrome.*
- *A screen positive result can be positive for either an NTD or for Down syndrome, occassionally for both, but can never serve to diagnose either disorder. This point cannot be overemphasized.*

syndrome and might provide useful clinical information for prenatal screening. In collaboration with the Foundation for Blood Research in Scarborough, Maine, and the Medical College of St. Bartholomew's Hospital in London, we showed that MSuE3 is, in fact, about 25 to 30% lower in Down syndrome pregnancy and that the measurement of MSuE3 along with MSAFP substantially enhances screening sensitivity.[5,6]

Since 1988, four studies have been published that confirm our findings that MSuE3 is low in Down syndrome pregnancy, with median values ranging from 0.52 to 0.74 multiples of the median (MoM).[7-10] In addition, we know of three as yet unpublished studies that also demonstrate the association. In contrast, Macri *et al.*, in a recently published paper,[11] were unable to find an association between low MSuE3 and Down syndrome pregnancy (median MoM = 0.99). It is not clear to us why this one study had negative results, but we feel that the group consensus median of 0.74 MoM (based on 320 cases), which includes the data of Macri *et al.*, will be found to be correct. The more significant issue of whether low MSuE3 will ultimately prove to be cost effective in prenatal screening for Down syndrome will be discussed later in this article.

Human Chorionic Gonadotropin

At about the same time that our research on unconjugated estriol was reported, Bogart *et al.* demonstrated that maternal serum levels of the placental hormone, human chorionic gonadotropin (hCG), were also abnormal in pregnancies affected with fetal Down syndrome.[12] The surprising finding was that MShCG levels were *higher* than normal, with an average concentration in samples from Down syndrome pregnancy approximately 2.5 times the level in unaffected pregnancies. Collaborative research, again involving the Foundation for Blood Research, the Medical College of St. Bartholomew's Hospital, and Women & Infants Hospital, confirmed this association and showed that the measurement of MShCG in combination with MSuE3 and MSAFP could better define patient-specific risk for fetal Down syndrome than any method previously described.[13] The median for cases in that study was 2.05 MoM.

The association between high MShCG levels and pregnancies affected with fetal Down syndrome has been replicated in a number of recent studies,[7-11,14-16] with median values ranging from 1.4 to almost 3 MoM. It is clear that MShCG is the most informative of the biochemical screening markers reported thus far, although as with MSuE3 the degree of separation between affected and unaffected pregnancies has not yet been established with certainty. As a matter of biology, it is interesting that all the pure placental secretory products studied thus far, including free alpha subunit, progesterone, human placental lactogen, and pregnancy-specific betal-glycoprotein, are higher than normal in maternal serum samples from Down syndrome pregnancies.[12-17]

Predicted Efficiency of Screening with Addition of MSuE3 and MShCG

The article by Wald *et al.* has provided a statistical method for the calculation of patient specific risk using MSAFP, MSuE3, and MShCG values in combination with maternal age.[13] A model of the distributions of risk values for both the affected and unaffected populations, obtained by using this statistical method on the data reported by Wald et al., is shown in Figure 1. It is important to note that this model describes the risks for pregnant women of all maternal ages. Therefore, the initial positive rates and detection rates that are calculated are for all pregnancies as a group, regardless of maternal age.

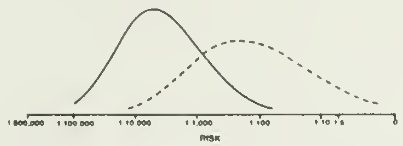

Figure 1. The relative frequency distributions of second trimester risks calculated for fetal Down syndrome and unaffected pregnancy using maternal age plus MSAFP, MSuE3, and MShCG, in combination. Solid line, distribution for unaffected pregnancy; dashed line, distribution for Down syndrome pregnancy.

At a second trimester risk for fetal Down syndrome of 1 in 190 or greater, which corresponds to a term risk cut-off of 1 in 250, the initial positive rate is predicted to be 5.0% with a detection rate of 61%. If a second trimester risk cut-off of 1 in 270 is selected (term risk = 1 in 350), the initial positive rate is predicted to be 7.2% with a detection rate of 67%. If these predicted results hold true, the use of the three markers in combination will substantially enhance screening specificity and sensitivity as compared to the currently used method of age alone for older women and age plus MSAFP in younger women.

A recent study from Denmark by Norgaard-Pedersen *et al.*[10] confirms the findings of Wald *et al.*,[13] although at a 5% initial positive rate their detection rate would be lower (just over 50%). The Danish investigators raise the issue that the addition of MSuE3 is useful but that results using the two other markers without MSuE3 do not seem much inferior to the results obtained by using all three. The data in both studies, however, indicate that for a given detection rate, the initial positive rate is markedly reduced by the inclusion of MSuE3. In the study of Wald *et al.*, at a detection rate of 60% the initial positive rate decreased from 6.7 to 4.7% (a 30% reduction), and in the study of Norgaard-Pedersen *et al.*, at a detection rate of 50% the initial positive rate decreased from 6.0 to 4.3% (a 28% reduction, derived from data in the above study.[13] A reduction in the initial positive rate translates into a reduction in the amniocentesis rate. If, in fact, the inclusion of MSuE3 results in a 30% reduction in the amniocentesis rate, then the use of MSuE3 would be cost effective. Prospective studies using much larger numbers of samples are now underway and will soon provide more definitive answers.

The Screening Protocol

Enhanced screening for Down syndrome pregnancy is offered at Women & Infants Hospital as a clinical test called AFP PLUS (Figure 2). The test uses the same maternal serum sample obtained for routine MSAFP screening. Maternal serum uE3 and hCG are measured along with AFP and used in combination to increase or decrease a patient's age related risk for fetal Down syndrome. In addition, the AFP result is used as before to screen for open fetal defects. The screening protocol is as follows:

1. *A single sample of serum is obtained from a patient between her 15th and 20th completed week of pregnancy (ideally the sample should be obtained during the 16th week); 1-4 ml of separated serum is sufficient. The same sample will also be used for MSAFP screening for fetal open neural tube defects; a separate serum sample is not needed.*

2. *The test request slip must be filled out completely: a) Gestational dating information must be provided. If dating is by ultrasonography, the method of choice is biparietal diameter (BPD) measurement only. BPD measurement will enhance screening for open neural tube defects and will not be affected by fetal Down syndrome. b) Date of birth, maternal weight, and maternal race must be provided for proper interpretation of results. Maternal age is necessary to calculate patient-specific risk for fetal Down syndrome, maternal weight is necessary to adjust for differences in maternal dilution of the screening markers, and maternal race is necessary to adjust for the higher AFP levels in the black population. c) Relevant information on patient or family history of open neural tube defects or chromosomal defects must be provided for proper analysis of patient-specific risk. In addition, maternal insulin-dependent diabetes mellitus has been identified as a risk factor for open neural tube defects and must be indicated if present.*

A screen positive result with AFP PLUS is defined as a patient-specific risk of at least 1 in 270 for carrying a fetus affected with Down syndrome. The patient-specific risk is calculated by computer from the results of the assays for AFP, uE3, and hCG and from the age-associated risk. A cut-off of 1 in 270 is used because that is the second trimester risk of an unscreened 35 year old patient.

A patient whose risk of fetal Down syndrome by AFP PLUS is found to be less than 1 in 270 is considered screen negative. The particular risk after AFP PLUS may be lower or higher than the prescreen age-associated risk, but as long as the risk by AFP PLUS is less than 1 in 270, the test result is screen negative.

A patient whose results are screen positive should be counseled by her physician or by a genetic associate. These follow-up procedures should be offered:

a. *Confirmation of gestational dating by ultrasound measurement of BPD. If a pregnancy is not so far along as originally thought, the initial screen positive result might be screen negative after recalculation and reinterpretation.*

b. *If, after a check of gestational dating, the result remains positive, the patient should be counseled about the risk of fetal Down syndrome and offered amniocentesis.*

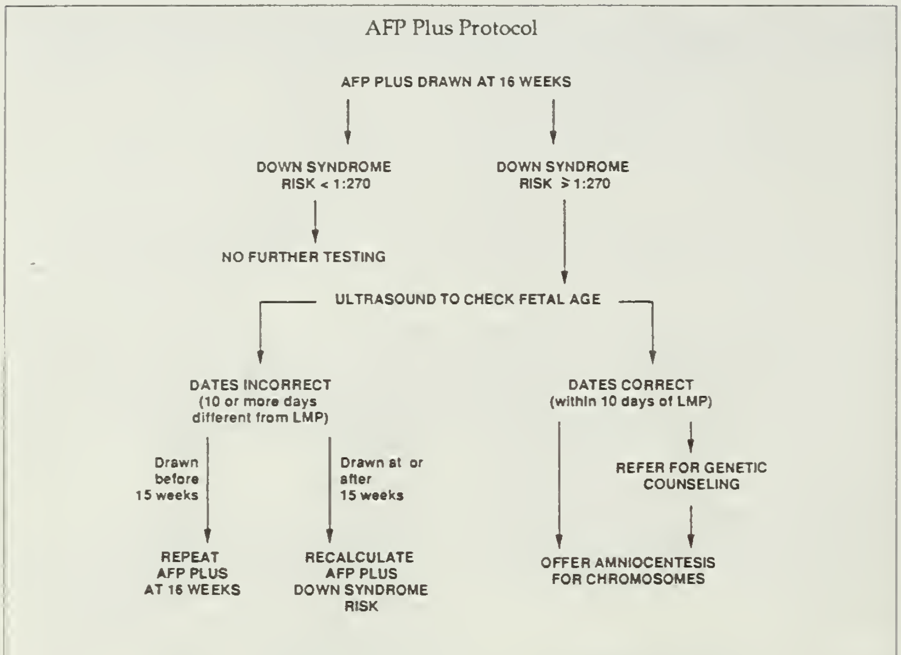
AFP Plus Protocol
AFP PLUS DRAWN AT 16 WEEKS
DOWN SYNDROME RISK < 1:270
DOWN SYNDROME RISK ≥ 1:270
NO FURTHER TESTING
ULTRASOUND TO CHECK FETAL AGE
DATES INCORRECT (10 or more days different from LMP)
DATES CORRECT (within 10 days of LMP)
Drawn before 15 weeks
Drawn at or after 15 weeks
REFER FOR GENETIC COUNSELING
REPEAT AFP PLUS AT 16 WEEKS
RECALCULATE AFP PLUS DOWN SYNDROME RISK
OFFER AMNIOCENTESIS FOR CHROMOSOMES

Figure 2. The AFP Plus Protocol used at Women & Infants Hospital

Detection of Other Chromosomal Disorders

The ability of the new method to enhance prenatal screening for chromosomal defects other than Down syndrome has not yet been demonstrated. However, information regarding the association between the individual markers and other chromosomal defects is becoming available. MSAFP is low in cases of fetal trisomy 18, with a median of 0.6 MoM.[18] Recently, we reported that MSuE3 is also low in trisomy 18, with a median of less than 0.5 MoM.[19] Bogart et *al.* initially reported on very low MShCG levels in two cases of fetal trisomy 18;[12] we have found that the median for hCG is less than 0.3 in trisomy 18 pregnancy.[19] Because MShCG levels are low rather than high in fetal trisomy 18, these pregnancies would most likely not be identified by a screening protocol designed to detect Down syndrome. A separate risk calculating system would have to be employed to identify individuals at high risk for trisomy 18. Levels of the new markers have not yet been found to be abnormal in any aneuploidies other than trisomy 21 and 18.

Who Should Have the AFP Plus Test?

With enhanced screening, maternal age becomes just one of four determinants of risk and can no longer be considered the prime screening variable. Therefore, all patients, regardless of age, can be candidates for screening. Specific considerations are as follows:

*1. **The younger patient:** All women who are currently offered MSAFP screening should be considered candidates for enhanced screening. Based on current criteria for screening, this number includes all women under the age of 35.*

*2. **The older patient:** Patients who are 35 or older are usually offered genetic amniocentesis and are not routinely offered screening by MSAFP alone. This is because MSAFP screening for Down syndrome in older women would fail to detect a substantial number of cases. With the advent of enhanced screening, the percentage of undetected cases (so-called false negatives) will be much lower. An estimated 85% of all cases of fetal Down syndrome will be found in the screen positive group, which will comprise only 20% of all patients who are 35 or older. Thus, 80% of all older patients could be reclassified as low risk and could avoid amniocentesis with no more than 15% of the Down syndrome cases in this age group being undetected.*

Issues In Genetic Counseling

Before screening, a careful explanation of the test is essential. The patient should understand that screening is performed for open neural tube defects (NTDs) and Down syndrome. A screen negative result cannot rule out these disorders but will indicate that the risk for NTDs is now below the background risk of the general population, and that the risk for Down syndrome is now lower than that of a 35 year old. In some patients the Down syndrome risk may be increased beyond the age-related risk but still be below the risk of a 35 year old and thus be reported as screen negative. A screen positive result can be positive for either NTDs or for Down syndrome, occasionally for both, but can never serve to diagnose either disorder. This point cannot be overemphasized.

Patients should be told that a screen positive result merely indicates the need for additional testing. If the screen has been based on last menstrual period (LMP) dating, the next indicated procedure is ultrasound examination to determine gestational age. Dates may have been incorrect and upon redating, the result may become screen negative or may show that the initial sample was drawn too early or too late for valid interpretation. If the initial screen was based on ultrasound dating or if the follow-up ultrasound indicated that the LMP dating was correct, amniocentesis for chromosome diagnosis should be offered. When the increased risk is for NTD rather than Down syndrome, a level II ultrasound examination is another option.

The risks and benefits of all follow-up procedures as well as the actual risk for the disorder in question should be discussed with the patient. Many patients believe their risk to be far higher than it actually is and will be relieved to hear that the risk is considerably lower than they had expected. Most important, one must provide reassurance to the patient that the vast majority of women with screen positive results will have unaffected infants. The extreme anxiety created by screen positive results can be alleviated to some extent by thorough explanation of the test before the time of screening and at each step of follow-up.

Although the standard of care remains to offer amniocentesis to women over age 35, some women in this age group may want to consider enhanced screening as a first step. It is imperative that the differences between the former and the latter be explained carefully. First, the patient must understand that enhanced screening can neither diagnose nor rule out Down syndrome. It can, however, alter the age-related Down syndrome risk. Should this risk remain unchanged or increase, the patient may then opt for amniocentesis. Should the risk decrease below that of a 35 year old, the patient may decide against amniocentesis but should be cautioned that a reduced risk does not entirely eliminate the possibility of Down syndrome. Second, the patient should be informed that women 35 and older are at increased risk for chromosome disorders other than Down syndrome and that enhanced screening will not provide information about their risk for these other disorders. It must be made very clear that a normal amniocentesis result will rule out Down syndrome and other chromosomal disorders, whereas a negative screening result can only reduce the Down syndrome risk below that of a 35-year-old. The woman who feels that she must be sure that Down syndrome is ruled out must not be led to believe that a screening test will serve to do this. ◆

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Early Amniocentesis

—Wayne A. Miller, M.D., Barabara Thayer, M.S.

Amniocentesis at 12 to 14 weeks gestation is a technique that is being increasingly used as an alternative to routine amniocentesis or chorion villus sampling (CVS) for fetal chromosome analysis. The appeal of early amniocentesis, as of CVS, is that results are available earlier in the pregnancy. Because the very high degree of accuracy of the cytogenetic testing on amniotic fluid cells is retained, the diagnostic dilemmas and patient anxiety, sometimes generated by inconclusive results obtained after chorion villus sampling, are avoided. Moreover, the risk for false positive or false negative diagnosis is extremely low.

From July 1985 through April 1989, 348 early amniocentesis samples were analyzed at the Prenatal Diagnostic Center (PDC). Of these samples, 147 were from patients who had early amniocentesis at the Prenatal Diagnostic Center. The remainder was laboratory samples accepted from referring obstetricians. A control group of 324 women who underwent amniocentesis at > 15 weeks during the same time period was matched for maternal age and physician. Forty-six percent of the PDC early amniocenteses were performed at 12 weeks gestation, 38% at 13 weeks and 14% at 14 weeks. Twelve percent of the referred early amniocentesis group was tapped at 12 weeks, 18% at 13 weeks, and 70% at 14 weeks.

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The success rate in obtaining an amniotic fluid sample at the PDC has been 97.3%, with four failed taps out of 149 attempted procedures. Two of these failures were secondary to uterine cramping, and one resulted from tenting of the membranes. Of these four patients, two patients were rescheduled and amniocentesis was successfully performed at 12 to 14 weeks gestation. Two patients chose to be deferred to > 15 weeks. Patients who schedule for early amniocentesis at the PDC have been deferred if gestational age is earlier than 12 weeks, if the bowel is overriding the uterus, if cramping is noticed before the procedure is undertaken, or if there is no placenta-free needle path. One patient was deferred because of the presence of a large subchorionic hematoma secondary to a failed CVS attempt, another because of the presence of a large fibroid. Most deferred patients are followed with ultrasound examinations at one week intervals and undergo amniocentesis during the 12 to 14 week period.

In the PDC early amniocentesis group, there were two cases (1.4%) that required two needle insertions to obtain the sample of amniotic fluid. In the PDC routine amniocentesis group, there were also two cases (1.5%) that required two needle insertions. In no cases in either PDC group were more than two needle insertions made.

The cytogenetic protocol followed at the Prenatal Diagnostic Center is to do chromosome count in 15 cells, structural analysis in five metaphases, and to cut two karyotypes. The average completion time in 1989 for routine and early amniocentesis cases was 12.45 days and 14.45 days, respectively. The longer completion time for early samples is attributed to the fact that smaller volumes of amniotic fluid are taken at amniocentesis and fewer cells are obtained to initiate tissue cultures. The guideline that has evolved is to withdraw 1 ml per week of gestation.

Of the total of 348 early amniocentesis fluids analyzed in the laboratory, seven resulted in requests for second samples because of cell culture failure or incomplete cytogenetic study. There were no cases of unexplained mosaicism or suspicion of maternal cell contamination, which would have necessitated retaps. In five of the seven cases, fewer than 15 counts from seven colonies were obtained, but preliminary results were available to patients. One of these samples was obtained at 11 weeks. Another, which was brown and had an alpha-fetoprotein (AFP) value of 16 Multiples of the Median (MOM), was a case in which fetal demise occurred shortly after amniocentesis. Of the two cases in which no cytogenetic results were obtained, one was an 11- week sample, and one was grossly bloody. If the two 11- week samples and the one brown and the one bloody sample are removed from the group of seven retaps, the retap request rate for a clear amniotic fluid sample obtained at 12 to 14 weeks was 0.86%. This rate can be contrasted to an approximate 0.1% failure rate for an adequate amniotic fluid sample obtained at > 15 weeks.

The rate of obstetrical complications within four weeks of the procedure in the early amniocentesis group was higher than the rate in the routine group. Of the early amniocentesis patients, 0.3% reported cramping versus 0.8% in the routine group; 2.1% reported fluid leakage versus 0.4% in the routine group; and 1% reported vaginal bleeding in comparison to 0% in the routine group. Of the 10 cases in which cramping, fluid leakage, or vaginal bleeding was reported in the early group, there were no spontaneous pregnancy losses.

Therefore, although the rate of obstetrical complications postprocedure may be higher with early amniocentesis, these complications seem likely to resolve.

The pregnancy loss rate in the early (N=348) and routine (N=324) amniocentesis groups was assessed. There were nine induced abortions (2.6%) in the early group and three (0.9%) in the routine group, numbers reflecting the higher rate of identification of fetal abnormalities in the early group. The spontaneous loss rates at less than 20 weeks, 20 to 28 weeks, and greater than 28 weeks were 2.3%, 0.8% and 0.3% for the early group and 0.3%, 0.3% and 0% for the routine group.

A much larger series needs to be examined and statistically analyzed before conclusions can be drawn on the precise level of risk posed to pregnancy by early amniocentesis. Experience at the PDC and other medical centers indicates that, after allowing for higher rates of spontaneous pregnancy loss at earlier gestational ages, the risk for pregnancy loss associated with early amniocentesis is most likely 1/100 to 1/200. This risk can be contrasted with the commonly accepted 1/400 risk generally associated with routine amniocentesis.

In the 288 cases in the early amniocentesis group for which follow-up information has been obtained, there were no discrepancies between cytogenetic results and phenotype. The total rates of birth defects in the routine and early amniocentesis groups were within the established background risk in the general populations. There were no differences between the early amniocentesis patients and the routine amniocentesis patients in type of delivery, or birth weights or APGAR scores of the babies delivered. Of note is the lower rate of pulmonary problems in the newborns in the early amniocentesis group than in the control group.

These data indicate that for patients who are anxious to get cytogenetic testing results earlier in pregnancy than is possible with routine amniocentesis, amniocentesis at 12 to 14 weeks is an alternative that can be very reasonably considered as one of the options currently available for prenatal diagnosis. Guidelines have been offered by the Prenatal Diagnostic Center to referring obstetricians and to patients on who may wish to consider early amniocentesis. Maternal age > 40, the diagnosis of a chromosome abnormality either in a previous child or in a previous pregnancy, the presence of a parental translocation, or risk for an X-linked genetic disorder in male offspring are suggested as indications for early amniocentesis. Currently, early amniocentesis patients make up 4.4% of the PDC clinical case load. Amniotic fluids obtained at 12 to 14 weeks gestation constitute 6.6% of the amniotic fluid samples processed in the laboratory. New techniques such as the polymerase chain reaction or microchemical techniques could make early amniocentesis more widely applicable for a variety of disorders in which DNA testing or biochemical analysis is performed.

A point of discussion has been that AFP measurement for detection of neural tube defects in the fetus is currently performed on routine amniotic fluid samples processed in cytogenetics laboratories. Available data indicate that amniotic fluid AFP testing at 13 and 14 weeks gestation is 98% accurate in ruling out an open spina bifida in the fetus.[1] For patients who have amniocentesis at 12 weeks gestation, the Prenatal Diagnostic Center reports AFP measurements with a caveat about accuracy, and recommends maternal serum AFP screening at 16 to 18 weeks.

As advancements in reproductive technology continue to take place, couples are being offered more choices for prenatal screening and diagnostic testing. Their decisions will continue to depend on the perception of risk for an affected child, the willingness to accept a level of risk to the pregnancy to obtain diagnostic information, and the personal context within which the risks and benefits of various procedures are weighed. Because of the advantages discussed, early amniocentesis is being offered and selected as a means for prenatal diagnosis with increasing frequency. ◆

Summary of Key Points

◆ *A much larger series needs to be examined and statistically analyzed before conclusions can be drawn on the precise level of risk posed to pregnancy by early amniocentesis. Experience at the PDC and other medical centers indicates that, after allowing for higher rates of spontaneous pregnancy loss at earlier gestational ages, the risk for pregnancy loss associated with early amniocentesis is most likely 1/100 to 1/200. This risk can be contrasted with the commonly accepted 1/400 risk generally associated with routine amniocentesis.*

◆ *Maternal age > 40, the diagnosis of a chromosome abnormality either in a previous child or in a previous pregnancy, the presence of a parental translocation, or risk for an X-linked genetic disorder in male offspring are suggested as indications for early amniocentesis.*

◆ *Available data indicate that AFP testing at 13 and 14 weeks gestation is 98% accurate in ruling out an open spina bifida in the fetus. For patients who have amniocentesis at 12 weeks gestation, the Prenatal Diagnostic Center reports AFP measurements with a caveat about accuracy, and recommends maternal serum AFP screening at 16 to 18 weeks.*

Ultrasound Frontiers: Transvaginal and Doppler Sonography

—Karen M. Ferroni, M.D., Avis Vincensi, R.T., R.D., M.S.

There can be little argument that real-time ultrasonography has revolutionized the practice of obstetrics. Recently, two new developments, transvaginal ultrasound and the application of doppler ultrasound in obstetrics, have added new diagnostic possibilities and have generated much excitement in the field of prenatal diagnosis and fetal maternal medicine.

Transvaginal Sonography

It is estimated that congenital malformations are present in approximately 6% of pregnancies and half of these are considered major. The detection of these major malformations is the ultimate goal of prenatal diagnosis. As technology and the expertise of sonographers have progressed, we have continued to add to the list of malformations that are possible to diagnose prenatally. Transvaginal sonography provides an earlier look at the developing fetus and greater opportunity to identify the abnormal fetus.

The use of a vaginal transducer has several advantages for both the patient and the examiner. Because a full bladder is not required, transvaginal sonography is usually described by patients as a more comfortable procedure. If an urgent examination is required, there is no delay while the patient drinks fluids to fill her bladder. Because the transducer comes within close proximity to the structures that are being studied, improved resolution and higher magnification are achieved.

The ability to visualize the embryo has also allowed us to correlate ultrasound images with the anatomic work of embryologists and in many instances to verify the sequential events of embryonic development. Much of this early work was undertaken by Ilan E. Timor-Tritsch, M.D.[1] Accurate pregnancy dating with transabdominal ultrasound is difficult before 6.5 weeks as the embryo can not be clearly visualized. With the use of transvaginal sonography, early embryonic structures can be seen clearly, and allow the possibility of accurate pregnancy dating before 6.5 weeks. Recently, Timor-Tritsch and his collegues have proposed a method of pregnancy dating that utilizes the presence or absence of various embryonic structures as landmarks for gestational dating.[2] More accurate pregnancy dating allows better evaluation of fetal growth and well being late in gestation.

Despite advances in imaging technology, evaluation of fetal anatomy before 12 weeks gestation with transabdominal ultrasound is of limited use. We now have the theoretic ability to track early embryonic development and determine whether it is proceeding normally.

This process has already been applied to diagnosis of abdominal wall defects. The timing of physiologic midgut herniation and its resolution was elucidated by Timor-Tritch in 1988.[3] This information was recently used to diagnose the presence of gastroschisis in a fetus at 12 and 3/7 weeks gestation.[4]

The presence of cystic hygromas in the fetus has been associated with several congenital malformation syndromes including Turner's and Noonan's syndromes, fetal alcohol syndrome, several aneuploidies and other rare disorders, but cystic hygromas may also be found in normal pregnancies. Thus the finding of cystic hygromas in the fetus carries with it a variable prognosis. The early diagnosis of cystic hygroma by using transvaginal ultrasound may allow a better understanding of the natural course of this malformation. Recently, Bronshtein and his collegues have reported eight cases of cystic hygromas diagnosed as early as nine weeks gestation.[5] It was noted that the presence of septations in the hygromas was associated with a poor outcome. Three of the eight pregnancles resulted in normal, viable pregnancies. All of these had demonstrated the presence of non-septated hygromas, which eventually resolved. Such information may allow us to provide earlier and more accurate prenatal diagnosis.

Transvaginal sonography has placed pelvic structures more easily within reach and allowed, in some instances, easier retrieval of ova for *in vitro* fertilization, simplified treatment of benign ovarian cysts and ectopic pregnancies. In the future this technology may allow selective termination of embryos determined to be abnormal when there is a multiple pregnancy.[6]

The utility of transvaginal ultrasound is not limited solely to the embryonic period. Later in pregnancy it can permit better visualization of fetal structures presenting low in the pelvis, an accurate view of the location of the placenta, and an assessment of cervical length.

Examination of structures low in the pelvis can be obstructed because of the symphysis pubis and the iliac crests. Proceeding to transvaginal sonography may allow enhanced

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imaging of these structures. Benacerraf and Estroff first described this technique in 1989. [7] They described two cases where intracranial anomalies were suspected, and the fetal position limited the ability to visualize the fetal head. By using transvaginal technique, accurate diagnosis of a choroid plexus cyst and a neural tube defect was made possible. Cranial measurements can be difficult to obtain in the third trimester as well. Application of this technique could prove very useful, allowing better estimations of fetal weight and gestational age.

Transvaginal sonography is now routinely employed to assess the cervix, lower uterine segment, and position of the placenta. Limitations of transabdominal technique can make accurate diagnosis of placenta previa difficult. Uncertainty can frequently be eliminated by using transvaginal sonography. Initial concerns about the possibility of inducing bleeding as a result of this examination have proven to be unfounded when proper precautions are taken.

Cervical incompetence is a common cause of pregnancy loss before viability. Cervical length can be accurately determined by using transvaginal transducers, allowing comparison to normal cervical length. [8] Serial measurments may also prove of benefit in patients at risk for premature labor.

Doppler

The availability of duplex scanning systems allows a nearly simultaneous ability to visualize fetal structures and to direct doppler flow probes. These systems, combined with the enhanced imaging of new scanners, allow major advances in the prenatal diagnosis of congenital heart disease. Doppler studies of blood flow through various fetal structures as well as the uterine arteries have allowed new methods of studying fetal and maternal physiology in normal and abnormal states.

Key Points

◆ *The ability to visualize the embryo has also allowed correlation of ultrasound images with the anatomic work of embryologists and in many instances verification of the sequential events of embryonic development.*

◆ *The utility of transvaginal ultrasound is not limited solely to the embryonic period. Later in pregnancy it can permit better visualization of fetal structures presenting low in the pelvis, an accurate view of the location of the placenta, and an assessment of cervical length.*

◆ *Doppler studies of blood flow through various fetal structures as well as the uterine arteries have allowed new methods of studying fetal and maternal physiology in normal and abnormal states.*

Improved imaging technology has allowed better viusualization of fetal cardiac structures and permitted the prenatal diagnosis of many forms of congenital heart disease. Doppler flow measurements have allowed a better understanding of fetal cardiophysiology in both normal and pathologic states. It was doppler flow measurements that convinced fetal cardiologists that the fetal heart could increase stroke volume by augmenting ventricular filling, not just by increasing heart rate as had been previously thought. [9]

Indomethicin has been advocated as an effective drug to inhibit premature contractions. It is known that this drug also causes closure of the ductus arteriosis in newborns, and there have been concerns that ductal blood flow could be impeded in the fetus. Doppler flow measurements across the ductus have allowed proper monitoring of the fetus during administration.

A doppler flow measurement can be obtained from the ventricle just beneath the atrioventricular (AV) valve. In a fetus with structural heart defects, the presence of regurgitation across the AV valve suggests a poor prognosis, and is thought to be associated with fetal cardiac decompensation. [10]

The newest doppler technology is the use of color flow mapping. Blood flow towards the transducer is depicted as red, flow away from the transducer is blue. Blood flow through the cardiac chambers and great vessels is therefore seen in color, in real time. The resulting images are particularly useful in demonstrating abnormal shunting between the cardiac chambers. In the future, color flow mapping may play a larger role in prenatal diagnosis of congenital heart disease.

Although doppler measurements can be invaluable to the study of the fetal heart, the noncardiac applications are most common in obstetrics. Continuous wave or pulse doppler measurements of bood flow through the umbilical and uterine arteries are easy to perform and have significant clinical impact. Early reports recommended continuous doppler measurments as a method of assessing fetal well being and determining pregnancies at risk for adverse fetal outcome. This procedure has since been verified in several institutions and has begun to take its place as a standard method of fetal surveillance. Doppler flow measurements of the fetal umbilical cord have proven to correlate well with fetal acid-base status. Normally there is persistent blood flow through the umbilical artery even during diastole. As placental resistance increases, this diastolic flow diminishes and in severe cases may be be eliminated or reversed. By calculating the ratio of peak systolic flow to end diastolic flow (S/D), a measurement can be obtained that reflects placental resistance. An elevated S/D ratio correlates well with the presence of intrauterine growth retardation (IUGR), intrauterine fetal distress, and adverse neonatal outcome. When doppler measurements are combined with standard modalities for fetal surveillance such as non-stress testing and biophysical profile, more accurate determination of fetal status may be possible.

Doppler studies are also contributing to our understanding of fetal blood flow distribution in normal and abnormal states. Fetal cerebral vessels can be visualized and doppler measurements obtained from specific sites. [12] This visualization may provide information on cerebral blood flow in normal and growth retarded pregnancies, and may lead to greater ability to discriminate the IUGR fetus from its appropriate-for-gestation counterpart. Doppler measurements of the fetal renal artery have also been found to be altered in the presence of IUGR. [13] Studies such as these may increase our understanding of the pathophysiology of chronic intrauterine fetal distress and allow intervention before irreversible fetal damage.

Umbilical artery doppler flow studies may also be useful in the prenatal diagnosis of congenital anomalies. Several authors have reported the association of elevated S/D ratios and congenital anomalies in fetuses that demonsrate appropriate size for gestational age. Rochelson and Schulman noted that in 11 fetuses with abnormal karyotypes, nine demonstrated abnormal velocimetry, and in two of these fetuses, growth was normal. [14] It is interesting to note that, in these two pregnancies, amniotic fluid volume was abnormally increased. Meizner described umbilical and uterine blood flow measurements in 32 pregnancies complicated by major fetal anomalies. Seventeen of these demonstrated abnormal umbilical artery wave form patterns. The most common malformations in this group were CNS (13 of 32), followed by gastrointestinal urinary tract, and others. [15] It has since been suggested that routine use of umbilical velocimetry may help in screening for these anomalies.

Our improved ability to accurately assess gestational length, fetal growth and anatomic development, and pregnancy well-being have greatly influenced clinical decision making in obstetrics. These are exciting times in the field of prenatal diagnosis, and future developments hold the promise of increasing our knowledge and abilities in ways that we have not yet foreseen. ◆

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Chorionic Villus Sampling (CVS) Update

— *Miriam Schoenfeld DiMaio, M.S.W., Maurice J. Mahoney, M.D.*

Twenty-five years ago, Steele and Breg opened the door to prenatal diagnosis when they reported the successful determination of the karyotype of a human fetus by analyzing cultured amniotic fluid cells.[1] Mid-trimester amniocentesis soon became a common prenatal diagnosis procedure as its high degree of safety and accuracy became established. However, for many women, the benefits of amniocentesis have been overshadowed by the relatively late gestational age at which the procedure is performed. Efforts to accomplish prenatal diagnosis in the first trimester through analysis of placental tissue by chorionic villus sampling (CVS) began experimentally on pretermination patients in the 1960s and was first applied clinically in the 1970s in China for the purpose of prenatal sex determination.[2] In 1983, a method of CVS was developed which reliably provided sufficient quantities of chorionic villi to allow first trimester prenatal diagnosis of disorders lending themselves to cytogenetic, biochemical and DNA-based analyses.[2] CVS was then able to offer a woman the advantages of fetal diagnosis early in pregnancy, privacy about her pregnancy during the testing process and, in the event of abnormal results, the option of abortion in the first trimester. CVS is usually performed between 9 and 12 menstrual weeks of gestation but chorionic villi can be sampled at any time thereafter. A few perinatalogists are experimenting with CVS at 6 - 8 weeks gestation. Two approaches can be used to obtain the chorionic villi. The transcervical approach is performed using a flexible plastic catheter introduced through the vagina and cervix into the chorionic villi with ultrasound monitoring. The transabdominal approach uses an ultrasound-guided needle (19 or 20 gauge) in a manner analagous to amniocentesis. In the first trimester, placental and uterine position may influence the choice of which approach to use. In later pregnancy, only the transabdominal approach is employed.

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In 1983, shortly after the introduction of CVS into the United States, efforts to monitor the safety of the procedure were initiated through voluntary reporting of CVS experience by investigators around the world to a central data base; this data base has recorded over 50,000 transcervical CVS procedures.[3] However, the reporting was informal and no controlled studies were available to assess what proportion of miscarriages could actually be attributable to CVS. Assessment of risks of miscarriage associated with CVS was complicated by a number of factors including a poor understanding of the natural rate of pregnancy loss in sonographically normal-appearing fetuses in the late first and early second trimester. Furthermore, there was no systematic way of investigating the diagnostic accuracy of the procedure and the possibility of any long term harmful effects. In order to address these questions, the National Institutes of Health in 1985 sponsored a controlled study of the safety and accuracy of transcervical CVS at seven medical centers in the United States which already had established CVS programs.[4]

The safety arm of the study involved a cohort of 2278 women having CVS between 9 - 12 weeks of gestation whose experience was compared to a demographically similar group of 671 women having amniocentesis. All women were enrolled in the study in the first trimester, had a sonographically normal appearing pregnancy at the time of enrollment, and had maternal age as the only indication for prenatal diagnosis. Prior to 16 weeks of pregnancy, excess pregnancy loss among the women having CVS was found to be 0.8 percent. This analysis takes into account the fact that among the women not having CVS, karyotypically abnormal fetuses (which would have been identified by and electively aborted after CVS) are more likely to spontaneously miscarry. Loss rates in the two groups of women between 16 weeks and term were comparable. Although pregnancy loss attributable to CVS undoubtedly occurs beyond 16 weeks, this rate appears comparable to losses attributable to amniocentesis, which is estimated from previous studies at 0.5 - 1 percent. An overall risk of pregnancy loss attributable to CVS (when performed by an obstetrician experienced with the procedure) is estimated at slightly greater than 1 percent. These findings were further supported by similar results obtained from a randomized clinical trial of CVS and amniocentesis which was carried out in Canada.[5]

A number of factors were found to be associated with fetal loss after CVS, including placental position, the number of passes of the catheter, and the occurrence of vaginal spotting or bleeding prior to the procedure. No cases of serious maternal infection were reported in any of the women having CVS in this study. Infants born to participants in the study all had physical examinations during the first year of life. Only preliminary analysis of the infant data has been accomplished. This showed very similar gestational ages at birth, birth weights, and low frequency of birth defects in the babies whether their mothers had had amniocentesis or CVS.

The initial United States collaborative study and the Canadian study investigated only transcervical CVS. While these studies were being carried out, transabdominal CVS was increasingly adopted as an alternative approach with the suggestion that it might prove easier to learn and safer by virtue of less infection. A second NIH sponsored study with eight participating centers was commenced to assess the newer approach. The study has only recently been completed and initial results reported at the 1990 annual meeting of the American Society of Human Genetics.[6] The study randomized 3998 women between transcervical and transabdominal CVS whose indication for CVS was maternal age. Again, no instance of serious maternal infection occurred in either group. Both approaches proved equally safe and efficacious. Over 97 percent of women could have CVS successfully performed by either approach and, with both approaches available, close to 100 percent of women would have a successful CVS. There were no important differences in fetal loss rates, minor complications, birth weights, or gestational ages at delivery. The fetal loss rate was 0.8 percent lower than the loss rate recorded in the CVS group in the earlier comparison of transcervical CVS and amniocentesis. One significant difference between the two approaches was the sample size of villi. Median weight of chorionic villi obtained transabdominally was 20 mg and transcervically was 25 mg. Successful karyotyping did not differ and was accomplished in almost all cases.

Summary of Key Points

- ◆ *The ability of amniocentesis and* ***not*** *CVS to detect open structural body disorders in the fetus by qualification of amniotic fluid alpha-fetoprotein (AFP) remains the major diagnostic distinction between the two procedures.*
- ◆ *An overall risk of pregnancy loss attributable to CVS (when performed by an obstetrician experienced with the procedure) is estimated at slightly greater than 1 percent.*
- ◆ *As of Summer 1991, a controversy has arisen that questions the possibility of CVS causing major limb reduction or other disruption-type birth defects.*

The accuracy of CVS as a diagnostic method was also investigated in the two NIH sponsored studies and the results are encouraging. Over 10,000 women having CVS were included in this aspect of the two studies and a cytogenetic diagnosis was achieved for 99.6 percent. There were no incorrect predictions of fetal sex or diagnostic errors involving the autosomal aneuploidies or major cytogenetic structural abnormalities.[7]

The interpretation of cytogenetic results obtained following CVS is not always unambiguous. To understand the complexity of the interpretation of the karyotype obtained from chorionic villi, an appreciation of the embryology of this tissue is useful. The chorionic villi develop shortly after differentiation of the blastocyst and are comprised of a trophoblastic epithelium covering a central mesenchymal core. Although the cytotrophoblasts and mesenchyma are all descended from the original fertilized egg, the cells destined to become these structures diverge from the embryonic cell mass at a very early stage of development. Cytotrophoblasts are exclusively extraembryonic tissue and arise from cells that also become the yolk sac, placenta and membranes. In the mesenchymal core are cells that are of both embryonic and extraembryonic origin.

A karyotype can be obtained directly from the villi by recovering actively dividing cytotrophoblasts. Cytogenetic studies can be accomplished within hours to a day or two following sample acquisition. Likewise, DNA or enzymes can be extracted immediately. During the culturing process which takes 4 - 10 days, the cytotrophoblasts are eliminated and the analyzed cells are exclusively from the mesenchyma and therefore are more likely to be representative of the fetus.

Although the accuracy of CVS is comparable to amniocentesis for the purpose of diagnosing chromosome abnormalities, discordance between the karyotype obtained from "direct" analysis of the cytotrophoblast and that of cultured cells derived from the mesenchymal core occasionally poses interpretative problems. This occurs when chromosomal mosaicism is observed in one analysis and is absent in the other. Mosaicism is the presence of two or more cell lines with different karyotypes. This phenomenon is a result of a mitotic error that has occurred in one tissue but not the other. As expected, the finding of mosaicism in cultured cells is far more predictive of the chromosomal status of the fetus than the finding of mosaicism in the direct analysis of cytotrophoblasts. These observations have recently led most laboratories to rely exclusively on the analysis of cultured cells or to analyse both cultured cells and cytotrophoblasts.

Mosaicism in cultured chorionic villi occurs (is identified) in approximately 0.5 - 1 percent of cases; this compares with 0.2 - 0.3 percent in amniocentesis. When mosaicism is found, additional studies such as sonographic imaging and amniocentesis or fetal blood sampling are usually performed in order to obtain more information about the fetal karyotype. In about 40 percent of cases where mosaicism of cultured villi is detected, mosaicism for an abnormal cell line is also documented in fetal tissue or in the newborn; in amniocentesis experience this correlation is about 70 percent. In the remaining cases mosaicism is believed most often to be confined to the placenta although its undetected presence in the baby cannot be strictly excluded. For these patients, an increased risk of intrauterine growth retardation and perinatal loss has been observed suggesting that the abnormal cell line plays a role in causing placental dysfunction. Initial reports suggest that the fetal loss rate may be as high as 17 percent in pregnancies with placental mosaicism.[8] The mechanism by which the abnormal cell line contributes to placental dysfunction is not yet understood. It is likely that effects will depend on the specific abnormality and the percent of abnormal cells present. Just as mosaicism in chorionic villi or amniotic fluid cells will not always be present in the fetus, it is possible that mosaicism in the fetus, even with a very large percentage of abnormal cells, will not be present or documented (i.e., the abnormal cell line not be identified) in villi or amniotic fluid cells. Experience suggests that such false negative diagnoses will be rare in either method of prenatal diagnosis.

In common with fetal chromosome abnormalities, the accuracy of CVS and amniocentesis is generally comparable for diagnosing diseases based on enzyme or DNA analysis. The ability of amniocentesis and not CVS to detect open structural body disorders in the fetus by quantitation of amniotic fluid alpha-fetoprotein (AFP) remains the major diagnostic distinction between the two procedures. Maternal serum AFP screening at 16 weeks gestation is therefore recommended for all women having CVS.

In later pregnancy, when information about the karyotype is desired, transabdominal CVS may sometimes have advantages over amniocentesis or fetal blood sampling. Such instances include pregnancies in which amniotic fluid volume is severely decreased or absent, pregnancies in which ultrasound documents structural abnormalities of the fetus and fetal blood sampling is not successful or thought to be contraindicated, and pregnancies at very advanced gestational ages in which case amniocytes grow very slowly and a rapid karyotype of the fetus is desired.

As CVS increases in popularity, efforts are also underway to perform amniocentesis earlier in gestation. Initial reports about the safety and accuracy of late first trimester and early second trimester amniocentesis are encouraging. A number of questions remain to be answered including an accurate assessment of the fetal loss rate, other possible risks to the fetus of withdrawing a proportionately greater amount of amniotic fluid, and whether quantitation of amniotic fluid alpha-fetoprotein (AFP) and other amniotic fluid enzymes for the detection of open body defects is diagnostic at this stage of pregnancy. Future controlled studies will be necessary to answer these questions. ◆

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CVS and Birth Defects ?

This year Firth *et al*, from Oxford, England, reported 5 babies with transverse limb reductions, 4 of them with small jaws and tongues. The Oxford group had performed 539 CVS procedures and the babies with the problems had been in a subset of 289 pregnancies sampled before 9.5 weeks. Interruption of embryonic blood supply at a crucial time was offered as an hypothesis to link the defects to CVS. The US Collaborative studies found an incidence of limb reduction defects between 1 in 1000 and 1 in 2000, close to the incidence reported from large birth defect registeries (Mahoney *et al*, 1991). Further experience will be necessary to know whether CVS definitely poses a risk of disrubption-type birth defects, how high that risk might be, and what factors are important for minimizing or eliminating any risk.

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Fetal Blood Sampling

-Mary D'Alton, M.D.

Introduction

Practitioners in fetal medicine often have to rely on indirect clinical signs rather than on direct information to assist in patient management. Many decisions regarding management are based on fetal heart rate tracings and estimated fetal weight. In the past, when a fetal blood sample was necessary it could be obtained either by fetoscopy in the second trimester or fetal scalp sampling in the third. Both of these techniques have major limitations. Fetoscopy carries an inherent risk of 4 to 5 % of fetal loss and scalp sampling can be undertaken only after rupture of the membranes with adequate cervical dilatation. These limitations have impeded the use of these procedures. Over the last decade a new fetal blood sampling technique has been developed to obtain fetal blood. This technique it is currently being used for prenatal diagnosis.

Technique for Fetal Blood Sampling

In 1983, Daffos[1] first reported on the use of ultrasound-guided, umbilical blood sampling. This technique enables pure fetal blood to be obtained from approximately 18 weeks gestation and has proved efficient, rapid, and safe in experienced hands.[2] This technique has been referred to as percutaneous umbilical blood sampling (PUBS), fetal blood sampling (FBS), cordocentesis or funi puncture. This article will refer to the procedure as fetal blood sampling (FBS). FBS has become the procedure of choice to access fetal circulation. The basic techniques used for fetal blood sampling are a modifications of current amniocentesis procedures. FBS is an outpatient procedure. The following technique has evolved at St. Margaret's Hospital over the last five years.[3] Seconal (100 mg) is given to the pregnant woman one hour before the procedure for maternal sedation. A local anesthetic is used. A prophylactic antibiotic, dicloxacillin, is given to the mother one hour before the procedure and for 48 hours after. While some patients tolerate the procedure quite well with no sedation or anesthetic at all, it is our experience that because of the high level of maternal anxiety sedation is often useful. Our protocol does not involve the use any form of fetal paralysis for diagnostic procedures.

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To perform FBS, a sterile field is prepared and a sterile bag is used to cover the ultrasound transducer. A linear array transducer or a sector transducer may be used. The advantage of using a sector scanner is that the entire shaft of the needle can be visualized whereas only the needle tip can be visualised with the linear array transducer. However, the use of sector scanning has not increased the success rate of the blood sampling. In our unit, we use a 22-gauge spinal needle for all fetal blood sampling procedures while other institutions may use a 20 or 25 gauge. The umbilical vein is usually chosen as the vessel to sample because of its larger diameter. If fetal blood gas analysis is desired the syringe should contain a small amount of heparin. When the blood is obtained, it is important to ascertain whether it is fetal or maternal in origin. This differentiation is made by either of two techniques. Fetal cells are larger than maternal and a cell analyzer can be used to determine the mean corpuscular volume (MCV) of the sample and compare it to the size of known maternal cells. Performing an automated complete blood count (CBC) will demonstrate the mean corpuscular volume, although mixed samples will not be detected in this fashion. A cell analyzer that produces a frequency distribution of the cell sizes can assist in this process. The second technique is the Kleihauer-Betke stain, which relies on the tendency of adults cells to lyse in an acid environment in which fetal cells are still stable. The degree of purity of the sample can be measured by this method. The volume of sample removed depends on the indication. A complete blood profile, blood gases, and karyotype can be performed on one cc of whole blood. It has been our standard practice to take 3 cc across the gestational age span without any apparent side effects.

Fetal blood sampling is more difficult than amniocentesis in most instances. The physician with experience performing difficult amniocenteses, e.g., on patients with ruptured membranes, will have an easier time learning the method. In our experience performing 280 procedures, 84% of fetal blood samples have been obtained on the first needle insertion, 9.5% of cases have required two needle insertions, and 1.3% of patients have required three insertions. Our overall failure rate to obtain a sample is 4%. The entire procedure usually takes less than a half hour. If a fetal blood sample has not been obtained within this time, it is unlikely that the procedure will be successful. The majority of fetal blood sampling for diagnostic purposes is performed within 10 minutes.

Safety Considerations

The usefulness of any procedure is dependent on its safety. Most reports indicate that cordocentesis has a high margin of safety in terms of perinatal death.[2] The data, however, are difficult to interpret since many of the fetuses studied are severely ill at the time of the procedure. The background loss rate for this population is usually high in comparison with the population undergoing amniocentesis for karyotype or pulmonary maturity studies. Defining perinatal loss due to the procedure is difficult. For example, should a triploid fetus sampled at 25 weeks who dies *in utero* seven days after the procedure be considered a procedure-related loss? Currently, there is no consensus among investigators.

Key Points

- *Over the last decade a new fetal blood sampling technique has been developed to obtain fetal blood. This technique is currently being used for prenatal diagnosis...This technique has been referred to as percutaneous umbilical blood sampling (PUBS), fetal blood sampling (FBS), cordocentesis or funi puncture.*
- *It is conservative to state that the perinatal loss from cordocentesis is low, probably less than 1% plus the background risk to the fetus.*
- *Fetal blood provides information about normal fetal physiology that has not been available before.*

It is conservative to state that the perinatal loss from cordocentesis is low, probably less than 1% plus the background risk to the fetus. Over a five-year period in our personal experience of 280 cordocenteses, there has been one procedure related loss in a fetus with hydrocephalus at 18 weeks. The indication for the sampling procedure was fetal karyotype. Fetal death occured within 24 hours of the procedure. Postmortem examination failed to elucidate a cause for the intrauterine demise; specifically, there was no abruption, and no cord hematoma. The procedure had been considered uneventful. In our experience, two patients have also delivered within 24 hours of the procedure. In both instances, the fetal blood sampling was performed in twin gestations. Severe abdominal pain occured in one patient. The patient was observed in labor and delivery for a few hours after the procedure and the pain subsided. No cause was ever identified. The other potential adverse side effects consist of bleeding from the puncture site and transient fetal bradycardia. Our data reveal that bradycardia lasting for more than 60 seconds occurs in 4% of cases and that bleeding lasting longer than 60 seconds occurs in 5.4% of cases. Bradycardia appears to be significantly more common when the umbilical artery is punctured. For this reason the umbilical vein is the preferred target. Our data also show that there is a much higher risk to the fetus of an emergency cesarean section when fetal blood sampling is performed for the indication of intrauterine growth restriction.[4,5] We have performed sixteen cases of fetal blood sampling procedures for rapid karyotype in the setting of intrauterine growth restriction. The incidence of an emergency cesarean section, undertaken for severe variable decelerations in this situation was 25%.

It has been our experience that fetal blood sampling in general is a safe procedure; however, it carries with it a much higher risk of preterm delivery when performed in twin gestation and a much higher risk of emergency cesarean section when performed for the indication of intrauterine growth restriction.

Indications For Fetal Blood Sampling

The indications for FBS for both diagnostic and therapeutic purposes have grown rapidly. The most common indication for performance of FBS is the detection by ultrasound of a congenital malformation.

Fetal Blood Sampling Versus Amniocentesis

The likelihood of abnormal fetal karyotype when structural abnormality is detected antenatally with ultrasound ranges from 20 to 35%.[6,7] Few diagnostic procedures in the field of obstetrics offer such a high yield. The practice in our ultrasound unit is to offer some form of genetic analysis to all patients whose fetus has a congenital malformation (with the exception of gastrochisis). The method of genetic diagnosis selected depends on the gestational age of the fetus and the identified anomaly. It is our opinion that FBS ought to be performed shortly after the diagnosis of the malformation by ultrasound as the incidence of fetal demise associated with congenital anomalies is high. If fetal demise should occur and the postmorten cell culture fail, valuable information may be lost. If a malformation is detected at 18 weeks, FBS offers little advantage to amniocentesis. FBS will afford a diagnosis within 48 hours, whereas the karyotype will be available from amniocentesis within two weeks. If, for example, an anomaly is diagnosed by ultrasound at 22 weeks, the value of a rapid karyotype with FBS is obvious, offering parents accurate knowledge to make a decision regarding the pregnancy.

Other Uses for FBS

Hemolytic Disease

Since Liley's work was reported in 1963[8,9] measurements of the amniotic fluid optical density (OD) at 450 nanomoles (NM) has been the standard method for the evaluation of fetal hemolytic disease. It continues to have an important role, but, no longer an exclusive one. The problem with amniocentesis for OD 450 is that it remains an indirect assessment. At each given gestational age and optical density, the variation in fetal hematocrit is wide. Such variation is especially true in zone II of the Liley curve. Approximately 14% of neonates in zone II delivered between 34 and 37 weeks are unaffected, whereas 10% are severely affected.[8]

In general PUBS is used as an adjunct to amniocentesis. PUBS is performed in our institution in the following circumstances: 1) the indirect Coombs titre is 1 in 16 or higher and the patient has had a previous severely affected child, 2) the optical density result is in zone II, and 3) there is evidence of edema or fetal hydrops.

Fetal blood sampling is also offered to the Rh sensitized patient if the father is heterozygous. It is not known whether a single blood sampling procedure to prove that the fetus is Rhesus negative or several amniocenteses are the safest in this situation. In general most of our Rh sensitized patients decide to have PUBS for fetal blood group evaluation when the father is heterozygous.

Intravascular Transfusion

The following method is used for intravascular transfusion. Maternal sedation with seconal is provided to facilitate patient relaxation. Prophylactic antibiotics (dicloxacillin) as proposed for diagnostic fetal blood sampling are used. Tocolysis is not indicated. A 22-gauge needle is used, fetal blood sampling is performed to determine fetal hematocrit. During the wait for the hematocrit intravenous pancuronium, 0.1 mg per kilo of estimated fetal weight is injected intravenously into the umbilical vein where the fetal blood sampling is performed. If the umbilical artery is punctured, the needle is repositioned in the vein because of the high incidence of bradycardia that is associated with umbilical artery puncture. The operator ensures that the needle remains well positioned within the vessel lumen and a second person injects the blood. The packed cells are prepared from fresh donor blood compatible with both mother and fetus, washed and irradiated, and resuspended in normal saline at a hematocrit between 70 and 75%. A nomogram has been proposed to aid in the estimation of the transfused blood volume necessary to reach the target hematocrit.[12] A posttransfusion target is a hematocrit of 45 to 50%. A second transfusion may be necessary as early as one week after the first, depending on the percentage of fetal cells remaining after the transfusion and the closing hematocrit. After the second transfusion, the interval is spread out to three to four weeks. We perform our last transfusion between 34 and 36 weeks, and the fetus is delivered at term.

Hydrops Fetalis

The differential diagnosis for the etiology of hydrops fetalis is broad. Fetal blood should be taken for hematocrit, karyotype, and, in certain situations, hemoglobin electrophoresis and glucose-6 phosphate dehydrogenase deficiency.[13]

Congenital Infection

A negative maternal history does not exclude the possibility of congenital infection since many maternal episodes of infection are subclinical. Maternal serology may be misleading for a variety of reasons. First, the woman may persistently shed virus throughout pregnancy and fail to mount an immune response. Secondly, the available serologic methods may be suboptimal. Such is the case with toxoplasmosis, where in areas of low disease incidence an indeterminant result is common. The fetus may mount either minimal, transient or no immune response to toxoplasmosis, varicella, and parvo virus, despite the presence of symptomatic disease.[14,15] A high maternal IGG titer may mask the fetal IGM. A normal fetal IGM does not exclude congenital infection. It is important to supplement serology testing with other indirect measures such as platelet count, white blood cell count, and differential and liver enzymes. Experience with the difficulties involved in the accurate diagnosis of congenital infections is well illustrated by toxomplasmosis. Cultures of fetal blood and amniotic fluid, serology, hematologic and hepatic profiles, and ultrasound are all brought into play to make the diagnosis.[15]

Thrombocytopenia

There are two main fetal types of thrombocytopenia, autoimmune and alloimmune. Autoimmune thrombocytopenia is 10 to 20 times more common than alloimmune thrombocytopenia. Maternal idiopathic thrombocytopenia has been identified as a risk factor for neonatal intracranial hemorrhage. The degree of risk is not high as only a very small number of offspring will actually be thrombocytopenic themselves. Approaches to the disease have included use of maternal platelet counts, maternal antiplatelet antibody levels and fetal scalp blood sampling in labor. The first have proven inaccurate and the third requires adequate cervical dilatation and rupture of the membranes. Moreover, reports that fetal scalp sampling in labor gives an increased incidence of a falsely low count are discouraging.[16] We have found fetal blood sampling at term to be extremely helpful in the management of mothers with idiopathic thrombocytopenic purpura. The most common situation where we have seen abnormal fetal platelet counts has been when the mother has had a previous splenectomy for the treatment of her disease. In addition, the procedure has been of use in determining the site of delivery, for example, whether there is a need for the mother to deliver at a tertiary care center if a normal platelet count is present.

In neonatal alloimmune thrombocytopenia, fetal and neonatal thrombocytopenia results from the formation of a maternal antiplatelet antibody to a paternally derived platelet antigen, usually PLAl, expressed on the surface of the fetal platelets.[17] Immune thrombocytopenia may be thought of as Rhesus disease of the platelet. Ninety eight percent of the population have the PLA1 antigen. The fetus at risk is usually identified by the earlier birth of an affected sibling. Neonatal alloimmune thrombocytopenia occurs in approximately 1 in 2000 to 1 in 5000 fetuses. The exact incidence of intracranial hemorrhage among affected infants is not known, but estimates range between 10 and 30% of all cases.[17] The treatment of choice for alloimmune thrombocytopenia is transfusion of platelets lacking the incompatable antigen, which are usually obtained from the mother. Transfusion of unmatched platelets from a random donor may be helpful if matched platelets can not be obtained. Intravenous gamma globulin is also useful although corticosteroids are not considered to be effective.

Pilot studies have been conducted on the antenatal treatment of alloimmune thrombocytopenia.[17,18] Preliminary results indicate that intravenous gamma globulin with or without concommitant steroids increases fetal platelet counts in most cases and also seems to prevent intracranial hemorrhage even if it had occured antenatally in a previous sibling. A randomized controlled trial at Mount Sinai Medical Center in New York is underway. The purpose is to compare the use of intravenous (IV) gamma globulin alone at a dose of 1 gm per kilo per week to that of IV gamma globulin at the same dose plus low dose steroids. The study protocol requires that fetal blood sampling be performed before initiation of treatment and then again four to six weeks later to monitor the effectiveness of therapy. Under this study protocol for the antenatal treatment of alloimmune thrombocytopenia, the drug is provided free for the duration of therapy. Because of the rarity of this disorder, only collaborative efforts will arrive at optimal management schemes for patients with alloimmune thrombocytopenia.

It is of note that when we have performed blood sampling in the fetus, even in the face of an extremely low fetal platelet count (i.e., 10,000), we have not seen excessive hemorrhage. It is not our practice to have platelets ready to transfuse when fetal blood sampling is performed for auto or alloimmune thrombocytopenia.

Twin Preqnancy

It was our impression initially that the definitive diagnosis of Twin Transfusion Syndrome (TTS) could be made prenatally only by cordocentesis for fetal hematocrits.[19] Over a period of 18 months, it was our practice to perform cordocentesis if discordant fetal weights were demonstrated in a monochorionic gestation. In one of these cases, a woman with a twin gestation believed to be monochorionic had 1,000-g discrepancy between fetuses, noted at 28 weeks gestation. Cordocentesis was performed, revealing similar hematocrits and normal chromosomes studies for both fetuses. Serial ultrasounds were performed, and eventually pericardial effusion was noted in the larger twin at 34 weeks gestation. Both infants were delivered, and neonatal evaluation revealed an obvious TTS. TTS is a complex and dynamic physiologic state. Cordocentesis, however, deals only with a single hematocrit at one given moment. Cordocentesis with infusion of adult blood into the donor fetus has therefore been suggested in order to identify TTS. Subsequent cordocentesis performed on the larger recipient twin would then, in the presence of a significant communication, reveal adult hemoglobin. Caution is advised when considering the use of cordocenteses in twin gestations. Of 11 cordocentesis performed on twin gestations by the primary author, two women have delivered within 24 hours of the procedure. This result is in contrast to those for singleton gestations, in which preterm labor has not been encountered in over 280 cordocenteses.

Intrauterine Growth Retardation

A fetus with growth retardation is at increased risk for intrauterine death, fetal distress in labor, and asphyxia. Neonatal complications include asphyxia, hypoglycemia, and polycythemia. There is an increased incidence of chromosomal abnormality in infants with intrauterine growth retardation (IUGR). The knowledge of an abnormal karyotype in a patient with IUGR would significantly affect patient management. For instance, a fetus with a trisomy 18 would not undergo any other form of testing and cesarean delivery for fetal distress might be avoided. Traditionally, third trimester amniocentesis has been performed in fetuses with IUGR to rule out karyotypic abnormality. The length of time necessary for cell culture often makes the procedure impractical for use in clinical management. With the advent of percutaneous umbilical blood sampling, fetal blood can now be analyzed for karyotype within 24 to 72 hours. Fetal blood sampling also allows prenatal measurements of indicators of fetal acid base disturbance and hypoxia.

There is little in the published literature regarding the use of fetal blood sampling in the presence of intrauterine growth retardation. In 1987, Soothill published reports on 38 cases with IUGR.[20] IUGR was diagnosed if the abdominal circumference was less than the 5th percentile for gestational age. Fourteen of the fetuses demonstrated a venous oxygen tension below the 95% confidence limits. The outcome of the pregnancies and the perinatal testing that was performed on these fetuses was not addressed.

In 1986 Cox and Daffos reported results on 24 fetuses with IUGR less than the 10th percentile.[21] Seven fetuses demonstrated an abnormal pH when compared to the standard normograms. Five fetuses had decreased PO_2 and four fetuses had increased PO_2. The specific outcome of these fetuses with abnormal ph and gases *in utero* was not noted. In 1987, Pardi and colleagues reported on 14 pregnancies with a diagnosis of IUGR.[22] Twelve reliable fetal samples were obtained. Of those, eight patients had a cesarean section within eight hours of the sampling and six patients had an interval delivery. No chromosomal malformations were identified. The results of the cord gases and pH were known to the investigators although the authors commented that they did not affect management. It is interesting to note, however, that seven of the eight who had immediate cesarean section had an abnormal pH. Only one of the patients who had an interval delivery had an abnormal pH detected *in utero*.

Pearse and Chamberlain reported on 10 patients with asymmetric intrauterine growth retardation.[23] IUGR was defined as a head abdomen ratio greater than two standard deviations above the mean for gestational age. All 10 patients had pathologic tracings as defined by absence of variability or late decelerations seen on the fetal heart tracing. Eight patients were acidotic and needed a cesarean section.

We performed a study to determine the incidence of chromosomal abnormalities in IUGR in the absence of identifiable fetal anomalies on ultrasound and to correlate the intrauterine blood gas estimation with perinatal testing in the form of nonstress tests, biophysical profile, and doppler ultrasound. Intrauterine blood gas estimation was correlated with perinatal outcome. Of 16 IUGR fetuses two cases had major chromosomal abnormality. All of the other infants in the series survived. Nine demonstrated abnormal pH *in utero* as compared to normal control data. Fetuses with abnormal pH *in utero* may have a reactive nonstress test and normal biophysical, normal amniotic fluid volume, and normal doppler flow studies. Prolonged *in utero* survival is possible despite an abnormal pH or abnormal gases. Our data suggested an association between abnormal blood gas testing and neonatal hypoglycemia. We are continuing our investigation of cordocentesis to assess its role in the management of IUGR. Serious consideration must be given the high incidence of intervention related to the procedure. The cesarean section rate after fetal blood sampling for intrauterine growth retardation was 25% in our unit. Ongoing follow-up is in progress to see if those fetuses with hypoxia and acidosis *in utero* have different outcomes when compared with fetuses that have a normal intrauterine blood gas assessment. At the present time, we feel the only clinical role of fetal blood sampling in the presence of IUGR is to document fetal karyotype.[4,5] Until further knowledge is gained about blood gas interpretation *in utero*, we recommend that clinical management of the IUGR fetus should not be based on intrauterine blood gas assessment.

Research

Fetal blood sampling has allowed the performance of safe and direct evaluation of the fetus, and has enhanced the diagnostic and therapeutic abilities in fetal evaluation. In this article I have reviewed its role in various fetal conditions and its technique and safety.

Apart from the various uses of fetal blood sampling as a diagnostic tool, the potential for research is tremendous. Preliminary studies are supplying valuable information concerning fetal physiology and pathophysiology of a variety of conditions and fetal immunology. Blood and remaining fetal sera and plasma are frozen to evaluate fetal amino acids and fetal thyroid functions as an ongoing research venture. Fetal blood provides information about normal fetal physiology that has not been available before. ◆

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Fetal Cells in Maternal Blood: Prospects for Prenatal Diagnosis by Cell Sorting

— Diana W. Bianchi, M.D.

Amniocentesis and chorionic villus sampling are the currently accepted methods of obtaining fetal tissue for prenatal genetic diagnosis. Although these techniques are safe and accurate, they require trained clinicians to perform them and they carry a risk to the pregnancy. Many women (particularly those with a history of infertility) choose not to take the risk of a miscarriage related to an invasive diagnostic procedure. Additionally, most infants with autosomal trisomies are born to women under the age of 35. These women are generally not considered candidates for prenatal genetic diagnosis because the risk of the diagnostic procedure is greater than the incidence of the disease in that age group. A noninvasive method of obtaining information from fetal genes would revolutionize prenatal diagnosis. One approach, described elsewhere in this journal, is the alpha - fetoprotein "triple test," whereby specific proteins originating in the fetus or placenta are measured in the maternal serum. The relative values of these proteins are then compared with known trisomy 18 or 21 fetuses to give a modified risk for trisomy related to maternal age.

We have taken another approach. On the basis of previous studies documenting the presence of fetal cells in maternal blood, we have directed our efforts towards their identification and isolation. Although we are still at the research stage, we anticipate that these cells, obtained by maternal venipuncture, will have clinical utility as a source of fetal material for diagnostic tests.

Fetal Cells in Maternal Blood: History and Cell Types

Clinical studies of maternal-fetal blood group antigen incompatibility have shown that fetal erythrocytes and platelets cross the placenta and circulate within maternal blood.[1] Trophoblasts have been documented in maternal blood samples taken from both the uterine vein[2] and pulmonary veins at autopsy.[3] With the exception of trophoblasts, however, fetal cells cannot be distinguished from maternal cells by morphology alone. Before the era of cell sorting, Walknowska et al [4] screened the peripheral blood of 30 pregnant women and found metaphase spreads containing XY mitoses in 21 of them. Nineteen of the 21 women gave birth to males. The proportion of "fetal" mitoses visualized ranged from 0.2 to 1.5% in these phytohemagglutin-stimulated cells. This report created great excitement. The data were subsequently validated by another group.[5]

Lymphocytes and HLA-antigens

The screening of thousands of maternal metaphase spreads to find the rare fetal cell was labor-intensive. Thus, research efforts were directed towards developing methods that facilitated enrichment of the proportion of fetal cells present in maternal blood. At Stanford, Leonard Herzenberg pioneered the idea that the fluorescence activated cell sorter (FACS) could be used to physically separate fetal cells from maternal cells by using cell surface antigenic differences. His group used the presence of the HLA-A2 antigen on lymphocytes as a marker for fetal cells. Peripheral blood samples were obtained from 138 pregnant women and their spouses. Only women who tested negative for the HLA-A2 antigen with spouses who tested positive for the HLA-A2 antigen were sorted. The HLAA2(+) presumed lymphocytes were sorted onto microscope slides and analyzed with quinacrine fluorescence for the presence of the interphase Y chromosome.

There was a highly statistically significant correlation between the detection of the Y body in sorted cells and the presence of male sex and HLA-A2 antigen at birth (p value = 5.8 x 10-6, by Fisher Exact Test).[6,7] Although the use of uniquely fetal cell surface antigens and interphase Y chromatin provided two genetically independent means of identification of the cells as fetal, there were practical problems with the methodology. First, the maternal venous sample of 20 ml generated too few lymphocytes to be used clinically. Second, the fetal lymphocytes, although viable after sorting, could not be induced to divide. Third, because of the identification of paternally-derived HLA antigens, it was necessary to obtain paternal blood samples and do extensive HLA

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testing before fetal cell sorting. This procedure was difficult, time consuming, and expensive.

Trophoblast Cells: Lack of Specific Antibodies

Subsequent studies examined the possibility of sorting trophoblasts from maternal blood. Trophoblast cells were and remain attractive because they are uniquely fetal; their identification does not rely on paternal antigens. The monoclonal antibody, H315, was initially described as specific for antigens present on trophoblast cells. [8] One study[9] showed that there was a high percentage of H315(+) cells in the blood of pregnant women. Subsequently, this antigen was shown to be adsorbed by lymphocytes and therefore not specific for fetal cells. [10,11] The search for new antibodies that recognize trophoblast cells is an area of active research investigation.

Nucleated Erythrocytes

In our laboratory in the Division of Genetics at the Children's Hospital in Boston, we are studying the nucleated erythrocyte (NRBC) as a potential source of fetal genes. The NRBC, being nucleated, contains a full complement of genetic information. Normal pregnant females do not usually have circulating NRBC; therefore, an isolated NRBC is more likely to be fetal in origin. Physiologic changes occur over time in the percentage of nucleated versus nonnucleated erythrocytes present in the fetus. At 12 weeks of gestation, there are 50,000 NRBC per cubic millimeter of fetal blood, but at 20 weeks of gestation, there are only 1,000 NRBC per cubic millimeter. [12] The earlier peak is desirable for the application of this work to prenatal diagnosis. In any fetomaternal "transfusion," the ratio of fetal erythrocytes to fetal lymphocytes should remain the same as in whole fetal blood. Thus, 1,000 times as many red cells as white cells should be available for analysis. Finally, the recognition of fetal cells as "foreign" and subsequent clearance by the maternal immune system remain an obstacle to fetal cell isolation. Since the majority of pregnancies are blood-group compatible, it is likely that the NRBC will escape maternal detection and continue to circulate.

The Fluorescence-Activated Cell Sorter

The fluorescence-activated cell sorter (FACS) permits physical separation of living populations of cells.[13] Individual cells may be sorted on the basis of size, cell surface fluorescence, or both. As each cell enters the cell sorter, it is exposed to a beam of laser light, which excites fluorescent antibody molecules bound to cell surface antigens. As the cell passes through the laser light, it creates a light scatter that is converted to an electronic signal. The amount of signal generated is proportional to cell volume. A subsequent electronic signal records the amount of fluorescence present on the cell surface. If an individual cell possesses desired characteristics, such as fluorescence or a given size, an electric charge is applied to the cell, resulting in deflection into a collecting device. The FACS facilitates analysis and sorting of up to 5,000 cells per second, with a purity of 90 to 99%. Isolated cells may be deposited onto microscope slides for morphology or special stains. Alternatively, sorted cells may be collected into tubes or wells for subsequent culture or DNA analysis.

The FACS can also be utilized to separate individual chromosomes. This technique has been particularly useful in the establishment of chromosome-specific libraries for gene-mapping experiments. The principles of chromosome sorting are the same as in whole cell sorting. Fluorescent dyes that intercalate into DNA can be used to distinguish between individual chromosomes of different size. The amount of fluorescent signal generated is proportional to the amount of DNA present.

Detection of Fetal Nucleated Erythrocytes in the Blood of Pregnant Women: Preliminary Studies

To determine whether fetal NRBC was potentially useful as a fetal cell type for sorting, we selected monoclonal antibody against the transferrin receptor (TfR) to identify NRBC in the blood of pregnant women. The TfR antigen is a cell-surface glycoprotein necessary for iron transport. It is expressed on the surface of erythroblasts, tumor cells, activated lymphocytes, monocytes, and trophoblast cells.[14] Although TfR antigen is not specific for NRBC, our preliminary experiments indicate that it facilitates their enrichment in maternal blood. We have compared TfR(+) mononuclear cells sorted from peripheral blood samples for six pregnant women, six non-pregnant adults, and three umbilical cord bloods. We discovered that blood samples from pregnant women and umbilical cords contain significant numbers of recently enucleated and nucleated erythrocytes. [15] The TfR(+) cells in nonpregnant adults are monocytes and lymphocytes. The erythrocytes isolated from the pregnant women and umbilical cords contain fetal hemoglobin (HbF). The presence of HbF is suggestive but not conclusive that these cells are fetal in origin. To prove that the cells are fetal, one must show that they contain uniquely fetal gene sequences.

In our studies, we used the polymerase chain reaction (PCR) to amplify material from the Y chromosome. PCR creates multiple copies of a target gene sequence. Genetic diagnosis, therefore, is not limited by the small number of fetal cells found in maternal blood. Since Y chromosomal DNA is not normally present in the mother, we reasoned that any Y chromosomal sequences detected would have originated in the fetus. The presence of Y chromosomal DNA should therefore correlate with the birth of a male infant.

We studied 19 pregnant women at 12 to 17 weeks gestation. [15] Using the

Summary of Key Points

◆ *Most infants with autosomal trisomies are born to women under the age of 35. These women are generally not considered candidates for prenatal genetic diagnosis because the risk of the diagnostic procedure is greater than the incidence of the conditions in offspring of that age group. A noninvasive method of obtaining information from fetal genes would revolutionize prenatal diagnosis.*

◆ *The NRBC, being nucleated, contains a full complement of genetic information. Normal pregnant females do not usually have circulating NRBC; therefore, an isolated NRBC is more likely to be fetal in origin.*

◆ *The fluorescence-activated cell sorter permits physical separation of living populations of cells. Individual cells may be sorted on the basis of size, cell surface fluorescence, or both.*

◆ *Our data represent the first evidence that NRBC of fetal origin may be isolated from the peripheral blood of pregnant women.*

◆ *Fetal cells in maternal blood, although rare, represent an exciting prospect for future prenatal diagnosis.*

FACS, we sorted the TfR(+) cells from 20 ml of peripheral blood. The TfR(+) cells were lysed; the DNA was then amplified for a 222 base pair sequence normally found on the short arm of the Y chromosome. The 222 base pair sequence was detected on Southern blots from 6/8, or 75%, of the women who ultimately delivered males. To our surprise, the sequence was also detected in a sample from a pregnant woman with a female fetus. A blood sample was obtained from that same infant after birth; the 222 base pair sequence was again present. Although our results were consistent prenatally and postnatally (implying that we had indeed sorted fetal cells), it was of concern that the infant's phenotype and DNA analysis were discordant. Subsequent studies have included a normal physical exam, a normal 46,XX karyotype, and Southern blot analysis of unamplified infant DNA. We concluded that the infant appeared to have a very low level sex chromosome mosaicism or translocation of the Y derived sequence onto an autosome. It is also possible that the sequence was not entirely specific for the Y chromosome.

Despite these reservations, our data represent the first evidence that NRBC of fetal origin may be isolated from the peripheral blood of pregnant women. Our initial studies were undertaken at 12 to 17 weeks gestation. Currently we are analyzing samples from 8 to 10 weeks gestation to determine if a biologic "window" exists for the transfer of these nucleated cells from fetus to mother.

Future Clinical Uses of Fetal Cells Found in Maternal Blood

Since NRBC are obtained in a noninvasive manner from the mother, they have great potential usefulness in fetal genetic screening. If they can be isolated routinely from first prenatal blood samples, they may be deposited onto microscope slides and serve as a source of cells for in situ hybridization studies.[16,175] Currently, fluorescent probes exist that bind to chromosomes 13, 18, and 21. It is not difficult to imagine an automated test that would count areas of fluorescent hybridization as a prenatal screen for autosomal trisomies. Normally, two fluorescent "dots" would be present because of the two copies of each chromosome. Should three "dots" be detected, their presence would signal a pregnancy at risk for trisomy, and further counseling or diagnostic tests could be offered.

Alternatively, if the sorted population of fetal cells is shown to be free of contamination with maternal DNA, then this method has potential for detection of fetal gene mutations seen in such disorders as cystic fibrosis, phenylketonuria (PKU), Duchenne muscular dystrophy, and the hemoglobinopathies.

Finally, specific methods of erythroblast culture may result in metaphase spreads of sufficient quality to detect chromosome abnormalities.

Summary

Fetal cells in maternal blood, although rare, represent an exciting prospect for future prenatal diagnosis. The advantage of this technique is that venipuncture poses no risk to the fetus and may be performed in any medical setting. We have presented preliminary data showing that NRBC is one fetal cell type that can be sorted from maternal blood. Other investigators are working on lymphocyte and trophoblast cell isolation. The FACS facilitates the enrichment and purification of the fetal cells present in maternal blood; this permits fetal cell screening for autosomal trisomies or fetal gene analysis by amplification with the polymerase chain reaction. Although fetal cell sorting is still at the research stage, it appears that clinical application will be feasible within the next few years. ◆

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Psychological Adaptation to Pregnancy and Prenatal Diagnosis

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Pregnancy can be a time of change when a woman may experience many alterations in her sense of physiologic and psychologic well-being, physical appearance and self image, and role in society. Although modern obstetrics has done much to reduce the physical risks of childbirth, the psychological needs of the pregnant patient are often less well met.[1,2] Concerns about body image, motherhood, career, and financial security are among the many issues of concern to pregnant women. In addition to a woman's concerns about herself are questions regarding the fetus. Many pregnant women wonder about the infant and will try to envision the sex, appearance, and other attributes of the child to be.

Superimposed upon these very normal maternal reactions to pregnancy is often the concern over whether the baby will be healthy. This is a valid concern since as many as 20 to 25% of recognized pregnancies end in miscarriage or stillbirth, and 2 to 3% of all infants are born with major birth defects. Many pregnant women, however, are unaware of these statistics and enter the pregnant state with the expectation of a healthy infant. This is in contrast to the patient who has experienced a previous pregnancy loss or who has had a close association with an infant with congenital anomalies or heritable disease.

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Pregnant Women at Increased Risk

Expectant parents at an increased risk for a fetus with anomalies or those with a history of poor pregnancy outcome frequently require considerable counseling and reassurance. Such persons often enter into the pregnancy with some degree of acceptance of the a priori risk factors but will still exhibit an increased level of stress as a result of worries about possible fetal anomalies. Those women with a previously affected infant may come to the prenatal diagnosis process with considerable anxiety, as compared to those who elect amniocentesis for maternal age.[3] For some women at increased risk, any procedure that can help to reduce stress may be considered an important contribution to her psychological well-being. Recent research has shown that a normal amniocentesis can significantly reduce stress in the at-risk patient.[4] It is important, however, to understand that a woman at increased risk will have specific concerns that must be resolved before she can become fully comfortable with the pregnancy. Until the issue of recurrence risks have been resolved it is not unusual to see a delay in "bonding" and acceptance of the pregnancy.[5,6] A pregnant woman with a previous abnormal pregnancy may require additional reassurance even when she has been informed of a normal prenatal test result.[7]

One such patient identified with the concept of "being a little bit pregnant," a state of "pregnancy without expectation" of a having a child. The goal in such a gestation is to resolve this sense of ambiguity as rapidly as possible to permit a more normal psychosocial adjustment to the prenatal state. It is also important to facilitate grieving for any unresolved, unsuccessful gestations experienced by the pregnant woman.[8]

Pregnant Women at Decreased Risk

Most pregnant women enter pregnancy with every expectation of a healthy outcome. The majority of women have given little thought to prenatal diagnosis and potential implications of an atypical gestation unless a routine ultrasound or a maternal serum alpha-fetoprotein (MSAFP) drawn as part of standard prenatal lab work suddenly raises the specter of a potentially compromised infant. When an MSAFP result or ultrasound indicates a cause for concern, the woman and her partner are often initially in a state of shock, fearing that their baby has a serious, perhaps life-threatening problem that was totally unexpected. The expectant parents may find themselves being sent for additional testing with increasingly difficult decisions along the way. This scenario maybe accompanied by a poor understanding of the tests that have led to their being placed in a high risk group, or even of their actual risks for an affected pregnancy. It is an even more stressful situation if there has been little time to adapt to the concept of a problem pregnancy, and then suddenly there is a compelling sense of urgency. One perceptive patient described the events leading from a casually accepted MSAFP screen as "a roller coaster with no way to get off, each new test being an uphill climb leading to a deeper gut-wrenching chasm." Although this particular pregnancy ultimately resulted in a healthy infant, the couple had still not fully recovered from the experience by the time of their second pregnancy two years later. They opted *against* any form of prenatal assessment, saying they would rather take their chances than go through the same experience again. While this woman did say that she understood that MSAFP screening was a valuable tool, she wished that her first obstetrician had taken the time to discuss the purposes of the test and the possibility of an abnormal result before the assay was drawn. At the time of the MSAFP test she had not attached any more significance to it than to her other prenatal lab work until the nurse called her on a Friday afternoon to say her doctor was concerned about a possible birth defect in her baby and that she needed to come for an ultrasound the following week.

Key Points

- *Most pregnant women enter pregnancy with every expectation of a healthy outcome.*
- *It needs to be recognized that pregnancy is a time of considerable adaptation for a pregnant woman and her partner.*
- *A more complete discussion of the benefits of the MSAFP screening test, the very real potential for an abnormal result on the initial screen, and the availability of reliable diagnostic procedures may be helpful in reducing the stress associated with an abnormal screening test result and the subsequent evaluation.*
- *The increasing involvement by a more sophisticated patient in making informed decisions about pregnancy options and rapid advances in the field of prenatal diagnosis have not necessarily reduced the fears and anxieties associated with pregnancy and, in fact, may in some cases have actually interfered with the pregnancy experience and "bonding" patterns.*

Importance of Patient Education

Prenatal genetic tests are often poorly understood by the patient, and, in some instances by health professionals. Many are unaware of the distinction between a screening test and a diagnostic test. For example, MSAFP determination is a screening test; an abnormal result does not necessarily imply that the fetus is affected but rather that the pregnancy falls into a high enough risk group to justify more specific (and also more costly and potentially dangerous) diagnostic testing. In this regard MSAFP is similar to maternal age. A 35-year-old is offered an amniocentesis not to confirm Down syndrome but rather because her risk for the condition balances the risk of the procedure and the testing is considered cost effective. Most such patients can expect to receive a reassuring result. The same is true for the patient with an abnormal MSAFP, although such a patient will frequently be extremely anxious at finding herself at unanticipated increased risk.[9,10] Even after the abnormal MSAFP has been resolved, there may still be residual anxiety which must be addressed.[10] More than one patient has undergone amniocentesis because she cannot otherwise relieve the fear placed in her mind by an abnormal MSAFP, which was subsequently explained by ultrasonographic dating of the pregnancy. The more invasive yet also diagnostic amniocentesis was required to relieve the distrust introduced into the maternal-fetal relationship by the original MSAFP result.

The concept of a screening test should ideally be conveyed to the patient prior to the time of testing so that she is well aware of the potential for an abnormal result. Most women will receive a normal report from the screening, which may be a factor in reducing baseline prenatal anxiety and fostering a healthy attitude toward the pregnancy.[11,12] A more complete discussion of the benefits of the MSAFP screening test, the very real potential for an abnormal result on the initial screen, and the availability of reliable diagnostic procedures may be helpful in reducing the stress associated with an abnormal screening test result and the subsequent evaluation.

Psychological Adaptation

In most situations prenatal diagnosis continues to be performed during the second trimester. This timing is generally not optimal for a variety of reasons. While the first trimester may be more narcissistic in psychological adaptation with maternal concerns addressed more toward the mother's own changing physiology, the second trimester is usually associated with increasing awareness of the fetus as a separate entity.[1] This is also the critical period in prenatal diagnosis. Doppler auscultation of the fetal heart, visualization of very human features including the sex of the fetus by ultrasound, and quickening, the first awareness of fetal movement, all lead to the conceptus being seen as a person and thus increased vulnerability to maternal hopes and fears. A "bonding" may have taken place and the "pregnancy" or "fetus" has now become a "baby." The timing of this psychological investment into the pregnancy varies considerably from patient to patient, but with the current techniques, such a relationship is usually occurring when routine prenatal screening is introduced into the relationship. While ultrasound can be an enjoyable experience that most couples find to be fun after the initial concerns about the new experience, the expectant parents certainly react to the images on the screen, forming a picture of the baby in their mind.[13] The ultrasound visit often leads to "first baby pictures" for the family album, frequently almost unrecognizable to the uninitiated but still very precious in validation of the growing attachment to the new life. Conversely, ultrasound may not be a pleasant event for the couple who may come to consider the termination of a very wanted pregnancy. Under such circumstances, the demonstration of fetal anatomy and behavior can be very disconcerting. It is therefore important to verify the viability of the fetus and address any particular risk factors as early in the examination as possible.

The third trimester tends to consolidate fears regarding both maternal and fetal well-being as well as the realization that the woman's life is about to change forever as she takes on the new role of being a mother. Worries about labor and delivery emerge, expressed as concerns about pain and maternal injury as well as fears for the infant. Although such feelings are common as the end of pregnancy approaches, similar concerns may be initiated by amniocentesis, with questions regarding discomfort associated with the procedure and risks of injury to mother and infant. The father may also be involved and express concern for his partner and unborn child. This fear can make expectant parents tense and it is not unusual for the caregiver to sense anger, resentment, or conflict. Increased hostility and less somatic well-being have been demonstrated in patients undergoing amniocentesis, although this appears to resolve following the procedure.[14] It is important for the caregivers to understand that the expression of anger is usually not a personal affront but a response to the sense of entrapment by circumstances outside the couple's control, which usually resolves with reduction of anxiety regarding the pregnancy.

Summary

Overall, it needs to be recognized that pregnancy is a time of considerable adaptation for the pregnant patient and her partner. The increasing involvement by a more sophisticated patient in making informed decisions about pregnancy options and rapid advances in the field of prenatal diagnosis have not necessarily reduced the fears and anxieties associated with pregnancy and, in fact, may in some cases actually interfere with the pregnancy experience and "bonding" patterns.

The goal of prenatal diagnosis ought to be to provide answers to specific concerns and to offer reassurance whenever possible. As prenatal diagnosis in the first trimester becomes more readily available through early amniocentesis and chorionic villus sampling (CVS), earlier resolution of the conflicts associated with prenatal diagnosis may be possible and the issue of fetal well-being can be addressed during a psychologically more receptive period in prenatal adaptation. However, whenever a fetal anomaly is strongly suspected, regardless of the gestational age, timely confirmation is essential. Provisions also need to be made for adequate information, counseling and follow-up.[15-19] The couple who has experienced a poor pregnancy outcome ought to be given the opportunity to ask questions and verbalize their fears to facilitate adjustment to the loss. The value of peer support groups in decreasing the sense of isolation these patients often feel cannot be overestimated. ◆

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Prenatal Diagnosis and Pregnancy Options

Introduction

The availability of prenatal genetic screening and diagnostic tests raises profound personal and ethical issues for families with regard to childbearing. A woman who becomes pregnant today now has a variety of choices regarding whether or not to have a test and what to do with the information that will arise. The decision about whether or not to test is based on numerous factors in addition to the facts of the medical and family history. The contributing factors that may influence ones decision about prenatal diagnosis and pregnancy options includes ones personal beliefs, family support systems, religion, economic situation, existence of social and support programs, as well as ones attitude toward disability. While some prospective parents who learn their fetus has a disability may feel an inability to continue the pregnancy, others may feel differently. Obviously each individual has a unique set of circumstances giving rise to what they will ultimately determine is their best option. (With developments in ultrasonography and the advent of PUBS, there are an increasing number of women who learn late in pregnancy that their fetus has a disability and may have no options other than continuing the pregnancy).

For many individuals, parents and professionals alike, the concept of choosing to continue a pregnancy once a fetal disability has been identified may seem foreign. For others, it may be the most natural choice. However, for the majority of persons there will be some confusion about what to choice to make. This decision frequently needs to be decided upon within a short period of time. The information provided by the professional to the parent will frequently have a significant affect on the parent's decision.

When presenting an abnormal prenatal diagnostic test result some of the initial issues that providers ought to be prepared to raise and to discuss include: Why did this happen? What causes the disability? If the pregnancy is carried to term what will the birth be like? What special arrangements might be needed? What will the baby look like? Will the baby be mentally retarded? What medical/surgical procedures are available for treatment *in utero*? What is the kind of care that will be needed after the birth? How long can a person with this condition be expected to live? What types of medical, physical, and psychological issues might be expected? What lifelong management will there be? What community services are available to help the child after birth? What is the chance of this happening again? Do you know others who have had a child with this disability? Are their other parents that can be contacted?

Reproductive Alternatives: Issues in Decision Making

A woman's/family's response to an abnormal prenatal test result depends on a number of factors, including their concept of the disability, and their experience with disabled people. For some families, learning that the unborn child will have a disability does not in any way alter childbearing plans. For a very small number, the diagnosis of a fetal disability is the desired outcome; for others there is a certainty regarding pregnancy termination. For most people the news is usually upsetting, unsettling and disconcerting and may involve a great deal of anguish and thought. Many in this group may be truly undecided about what to do. For all, but particularly for this large group, there is an obligation to present all the options as clearly and thoughtfully as possible. There are several reasons for doing this including, 1) the decision is something families will live with for a lifetime, and 2) disability is a condition of life and it is a disservice to act in a way that is dismissive. It is crucial to help a woman/family make a decision that is right for the particular individual, without being judgemental of the community of people with disabilities.

Making a Referral for Prenatal Peer Support

Referring pregnant women who learn that their fetus has a specific disability to an established Prenatal Peer Support Program can be extremely useful in helping them to make a decision about the pregnancy. At present, one Prenatal Peer Support Program exists in Massachusetts and is modeled after the Parent to Parent Programs which are designed to provide support to families who have a family member with a disability. Parent to Parent programs match an experienced or "veteran" parent of a family member with a disability with a new, referred parent who is just beginning to meet the challenges of a disability within the family. Through the match, the veteran parent is often able to provide the referred parent with the unique emotional and informational support that comes from shared experiences. In the case of the Prenatal Peer Support Program of the Massachusetts Spina Bifida Association, the pregnant woman carrying a fetus with a disability (in this case, spina bifida) is referred to a parent of a child with spina bifida. This "Helping Parent" has been trained to sensitively provide information about raising a child with spina bifida. The helping parent is available to share her first hand experience and to answer any questions the pregnant woman (or couple) may have. The "Helping Parent" does not suggest a course of action for the pregnant woman but rather encourages the pregnant woman to gain some familiarity with the real life experiences of individuals and families with the disability. The role of the "Helping Parent" is to be non-judgmental and non-directive.

Responsibility of the Health Care Provider

In order to help facilitate a decision about an abnormal prenatal diagnostic result, health care providers need to be aware of the range of pregnancy options. In addition, sensitivity to the methods in which the information is conveyed is important, for the style of "information transfer" may have an obvious or subtle impact on the decision-making process. In addition to discussing pregnancy continuation as an option, this article describes the other options that ought to be raised with individuals who learn their fetus has a disability and it suggests general guidelines for presenting information about disabilities and pregnancy options.

Counseling about Pregnancy Options upon Receipt of Abnormal Prenatal Diagnostic Test Results

Guidelines for Health Care Providers

- Be prepared with accurate, up-to-date information and written materials about the specific disability.
- Present the range of alternative options (i.e., continuing the pregnancy, adoption, pregnancy termination).
- Recommend immediate genetic counseling for parents who are looking at pregnancy options. There are also other trained counselors who can assist parents in the decision-making process.
- Help parents obtain information quickly so that an informed decision can be made.
- Of parents who receive abnormal prenatal test results immediately prior to the weekend often need immediate counseling or, at the very least, a knowledgable professional to talk with. Arrange for information immediately for those who want it.
- If there are two parents involved it is important that each one be included in the discussions whenever possible.
- Have a list of contact people for all options, including parents who are raising a child with special needs, parents who have relinquished a child, or parents who have chosen to terminate a pregnancy.
- Offer yourself/office setting as a resource in order to help parents avoid red tape in accessing services or information.
- Provide parents with information about the local agencies and services that may potentially be needed for their child. Though eligibility requirements vary, many states provide some service to families who have a child with a disability. The may include case management, home and respite care, public health nurses, counseling, medical services, financial services, and special educaton programs.
- Maintain a listing of therapeutic counselors. It is crucial for some parents to be able to speak with an objective person who is not judgemental, who is sensitive to their feelings and specifically trained in perinatal grief counseling.
- Have names and numbers of agencies or organizations which focus on the provision of support for the decision that is finally made. For example, those that support parents who choose to raise a child with special needs, those that deal with special needs adoption, or those that provide support to parents who choose a termination.
- Be prepared to stay in touch with the parents and to offer continued support. Do not assume that a referral to a peer support program is providing everything the parents need.
- Recognize your own biases. Try to remain non-judgemental or refer parents to other professionals for care when necessary.
- Keep lines of communication open. Even if parents express a reluctance to talk at one time, they made need to talk at another time. Many parents appreciate the kindess professionals have shown by offering home telephone numbers.
- Do not make assumptions. Many parents who are viewed as "the perfect parent to handle a child with special needs" or those who you think might be apt to terminate the pregnancy may have a different view of themselves and may select an alternative not commonly expected.

OPTION 1:

Continue the Pregnancy, Raise the Child

-Marsha Saxton, Betsy Anderson, Robin J.R. Blatt

*Ms. **Saxton** is the Director of the Project on Women and Disability.*

*Ms. **Anderson** is the Director of the CAPP National Parent Resource Center at the Federation for Children with Special Needs. Both serve as Consumer Advisors to **The Genetic Resource**.*

***Robin J.R. Blatt** is the Education Coordinator of the Massachusetts Genetics Program, Massachusetts Department of Public Health and Co-Editor of **The Genetic Resource**.*

Some women will learn through prenatal diagnosis that they are carrying a fetus with a disability. Many parents will continue the pregnancy and raise the child, never considering any alternative. Others may carefully weigh the decision to continue the pregnancy or not, and take the maximal time, however limited, to make their decision. Health care providers have a responsiblity to make it clear that continuing the pregnancy is an option and that services and resources are sometimes available to assist the family to raise the child at home.

Factors that may affect the mothers' or parents' decision-making include: how the diagnosis and the nature ofthe disability is presented to them, wehther the child would be expected to die or have a shortened life span, the potential range of severity, whether mental retardation could be a factor, and the ethnic, religious, cultrual background and the economic situation of the family.

Practitioners must become aware of their own biases about abortion, about quality of life issues regarding certain disabilities, or about a particular mother or family's competence or ability to care for a particular child. The ethical mandate to remain unbiased cannot eliminate a lifetime of values development, opinions and beliefs that every individual holds. Most everyone, including the most responsible and skilled professionals, carrry such biases, admit it or not. Efforts by the individual pracitioner to bring these biases to consciousness through various reading or through self exploration, will enhance pracitioner's ability to provide the most effective assistance to families in their own decision making process.

The parent's decision, whatever it be, must be validated as their best thinking and their accurate assessment of their own resources and options.

Having a Child with a Disability

It is essential for parents to know that support systems such as health services, respite care, self-help and mutual aid groups, parent to parent connections, information and referral, early intervention programs, and financial planning and assistance are available. Of course all this information must be presented in a manner that refelcts the parent's receptivity to learn about and engage in interaction with services and other people, which may be a gradual process. Case management services are an important resource in helping parents to negotiate the maze of services, benefits and bureaucracy.

It is important for providers to take care not to communicate that the only experience of having a child with a disability is the difficult task of managing medical and special needs. The literature is full of parent's own accounts of the satisfaction, joy and fulfillment of raising children with disabilities and of the integration of children with disabilities into the family and community as an important and essential process of challenging discrimination and promoting diversity in our society.

The community of parents of disabled children has done an excellent job of organizing themselves both to lobby for increased services and rights for their children and for support and mutual aid for themselves as caregivers and parents. Parents who choose to raise a child with a disability are not "saints". Treating or complimenting them as "amazing" or 'courageous" ultimatley only serves to make the parents feel objectified. Parents of disabled children ought to be treated with the same respectful attitudes as any parent, namely that they are doing the best they can to express and demonstrate their skills and values and love for their children.

Parents with Disabilities

Of course, throughout history people with disabilities have had offspring. Inmost societies, disabled people with either genetically related conditions or conditions thought to be genetic were discouraged or prevented from considering parenthood. This was due to the assumption that disabled people should not procreate and produce offspring with their genetic traits, but also becuase it was assumed that they could not function competently as parents.

A number of factors have led to an increase in people with disabilities deciding, despite the social prohibition, to become parents. These people include those with severe disabilities, many with genetic or genetically related conditions, (such as spina bifida, muscular dystrophy, dwarfism, ostegenesis imperfecta, juvenile diabetes, or congential deafness or blindness). Factors contributing to this change include medical treatments, which have improved the longevity and quality of life for people with disabling conditions.

But of equal importance are the disability rights and Independent Living movements which have increased disabled people's participation in the community, and improved their sense of self-esteem and competence, and provided concrete resources to live independently in the community. The recent passage of the Americans with Disabilities Act demonstrates that people with disabilities are experiencing a new level of access to political and social strength and are activley challenging old assumptions and stereotypes. These forces have encouraged peopel with disabilities to pursue parenthood, indeeed to view themselves as potential parents just like anyone else.

The medical system is just beginning to grapple with some of the unique social and medical issues of disabled individuals who choose to become parents. Practitioners who, for the first time, are dealing with the prospective parenthood of disabled people may or may not face some unusual or complex medical concerns. But they as medical personnel may have to confront their own values and reactions to disabled people taking on parenthood and making their own choices regarding the use of prenatal technolgoies. For example, there have been instances of parents with congenital deafness who live and function in the separate language culture of the deaf community, who have considerd using prenatal testing to identify and abort a fetus **without** the gene for deafness.

On the other hand and much more common, many mothers or prospective mothers with disabilities or genetic susceptiblities have reported receiving subtle pressure from their practitioners to undergo prenatal testing, and possibly abortion of an affected fetus, the assumption being that it is irresponsible to produce offspring with disabilities. Sometimes this pressure has been substantial, such as threat of denial of health insurance.

People with disabilities may elect to use prenatal screening, just as any couple, but they may also reject the use of this technology on the basis that they would choose to continue the pregnancy of an affected fetus. Some will use the technology to gather information to help plan for the birth of an affected child.

Practitioners must remember that disabled people considering parenthood have had experience living with their own disability and have learned to cope with and enjoy life as disabled persons. The common assumptions of hardship, tragedy or suffering for disabled people or their families may be an inaccurate viewpoint for someone who has actually lived life with that disability. We have much to learn from disabled people about the experience of life with physical, mental or emotional differences, beyond cultural stereotypes.

The challenge for prenatal care providers is to have the same attitude of respect, support and validation for these parents in making their own choices, and relaxedly offering assistance in obtaining necessary referrals and services, as they do for parents who are non-disabled. The history of the medical system's paternal attitudes directed at people with disabilities warrant's practioners taking extreme caution in assuming that they know medically and socially what is best for a disabled patient. Practitioners must take time to learn about the full range of resources for people with disabilties, such as those in the Independent Living and self-help communities.

Case Management Services

Karen Ayers, M.S., L.C.S.W.,
Director
Case Mangement Services
Massachusetts Department
of Public Health

Case Management is a term that has been overused recently and conjures up diffrent images to different people, but it is a term health care professionals need to understand and one that parents of children with special health care needs will hear more and more. As defined by the Joint Commission on Accreditation of Hospitals,

"Case Management includes those activities aimed at linking the service system to a consumer and coordinating the various system components in order to achieve a successful outcome. Case Management is essentially a problem solving function designed to ensure continuity of services and to overcome system rigidity."

Families of children with special health care needs have expressed dislike for the term "Case Management" because they neither want to be considered "cases" nor do they want to be "managed." Nevertheless, it is important for professionals, when describing the option of continuing a pregnancy of a disabled fetus to a potential parent, to inform them of existing case management services and to validate the potential parents as competent in assuming responsiblity for the care of their potential child. Parents who learn that their fetus has a disability may need or want assistance and support at various times during the pregnancy (and after the birth) as they try to coordinate the indiviudalized services that their child may need.

In a family-centered case management system the case manager works in active partnership with the parents (or potential parents) in determining the level of assistance that may be needed to ensure that services reflect the needs of both the child and family. The assistance may be in the form of information and referral, advocacy, consultation, service coordination, or monitoring.

The ultimate outcomes of case management services include, 1) mazimizing the healthy growth and development of a child with special health care needs in a community-based system of care, 2) improved availablility of services 3) greater accessiblity of services, 4) continuity of services, 5) avoidance of duplication of services and 6) coordinated service planning among mulitple agencies.

For parents who learn that their fetus has a disability and choose to continue the pregnancy, or for those who learn at birth that their child has special needs, a case manager can help tremendously. Case managers work closely with parents, assist in parent empowerment, and encourage parents to take an active role in managing the individual system of care that they might need. For some parents, being referred to a case manager even during pregnancy can help the parent cope with the news and begin to prepare for the future.

Case Management Programs in New England

The following State Title V Coordinators for Children with Special Health Care Needs in the New England Region can be contacted for more information about Case Mangement services in your area.

CT
Jadwiga Goclowski, R.N., Ph.D., Director
Family and Reproductive Heatlh
Department of Health and Human Services
150 Washington Street
Hartford, CT 06106
203-566-5601

ME
Kathleen Burden
Health Program Manager
State House, Station #11
Augusta, ME 04333
207-289-3311

MA
Deborah Allen, Ph.D., Director
Division for Children with Special Health Care Needs
Bureau of Parent, Child and Adolescent Health
Massachusetts Department of Public Health
150 Tremont Street, 2nd Floor
Boston, MA 02111
617-727-5121

NH
Jane Hybsch, Chief
Bureau of Special Medical Services
Divsion of Public Health Services
Health & Welfare Building
6 Hazen Drive
Concord, NH 03301
603-271-4596

RI
Richard Bolig, Chief
Office of Children with Special Health Care Needs
Rhode Island Department of Health, Room 302
75 Davis Drive
Providence, RI 02908
401-277-2312

VT
Carol Hassler, M.D.
State Director of Children with Special Health Care Needs
Vermont Department of Health
P.O. Box 70
1193 North Avenue
Burlington, VT 05402
802-863-7338

Other Resources

Alliance of Genetic Support Groups
1001 22nd Street, NW
Suite 800
Washington, DC 20037
(800) 336-GENE

The Alliance of Genetic Support Groups is a national coalition of voluntary genetic organizations and concerned individuals and health professionals whose purpose is to develop partnerships among consumers with genetic conditions and providers of genetic services. Established in 1986 under the leadership of Joan Weiss, M.S.W., L.C.S.W., the Alliance is funded by the March of Dimes and Maternal and Child Health Program, Health Resources and Services Administration, Department of Health and Human Resources.

National Organization for Rare Disorders (NORD)
P.O. Box 8923
New Fairfield, CT 06812
800-999-6673

National Information Center for Orphan Drugs and Rare Diseases (NICODARD)
P.O. Box 1133
Washington, D.C. 20013-1133
(800) 336-4797

OPTION 2:

Relinquishing a Child for Special Needs Adoption

-Joanne Finnegan

***Ms. Finnegan** is the birth mother of a child with Down Syndrome who was relinquished within an open adoption system, and she is the parent of a six year old daughter. The author acknowledges the contributions of Dr. Carl Cooley and Ms. Martha Jean Madison.*

Adoption is an option that can be presented to women who learn that through prenatal diagnosis that their fetus has a disability. Until recently, adoption was not traditionally viewed as an alternative to be presented to parents primarily because many professionals were unaware of the availability of adoptive parents for children with special needs. Contrary to popular belief, there are families who are willing, able and even anxious, to adopt a child with special needs. Throughout the Untied States there exist specific organizations which counsel and assist parents who are considering relinquishing or adopting a child with a disability. For example, the Down Syndrome Adoption Exchange has, at any given time, a list of thirty to forty families, some of whom have been waiting several months to adopt a child with Down syndrome. There is a similar national group that places children with spina bifida. In addition, a number of adoption agencies exist that specialize in the placement of children with special needs.

Medical professionals may question the timing of offering parents the information about adoption. For parents who have received the diagnosis prenatally, the adoption option ought to be presented along with the choices to either terminate or continue the pregnancy. There is no perfect time for presenting options to parents who have already given birth to a child with a disability. In both situations, professionals can be prepared with information, and listen for cues from parents. While some parents ask for their options, others may be less likely to do so. Some professionals have expressed concern that parents may react with anger at the suggestion of adoption. However, parents who appear to be opposed to adoption initially may serious consider it at a later time. One couple, new parents of a baby with Down syndrome stated, "A genetic counselor mentioned adoption immediately after we heard the news, but we quickly refused to hear it." A few weeks later this same family decided to relinquish their baby.

Some people fear that giving parents a choice will make parents grab at adoption as a "way out" and they will choose this rather than take the necessary time to educate themselves, get to know their child and to overcome any associated grief. Janet Marchese, of the National Down syndrome Adoption Exchange, receives approximately 700 calls from new parents each year. In 1990, only 100 of these parents elected to place their child for adoption. Of the 55 calls she received from couples who had received the diagnosis prenatally, none terminated and 2 placed their child for adoption. Providing parents with their options allows them to feel some control over the situation which frequently seems so out of control.

When presented with the possiblity of placing a child with special needs for adoption, parents may question "What kind of people would want to adopt this baby?" or, "If I don't want to raise my own baby, who would?" Most families who adopt a child with special needs do so because they have a loving home and wish to share it with a child who needs a stimulating, warm environment. Many families have had experience with children or adults with disabilities and feel confident that they can provide the special care these children will require. Some may already have biological or adopted children with special needs and wish to provide siblings who share common challenges.

Parents who wish to adopt are screened by a public or private state-licensed child welfare agency. A home study is performed by which the adoption agency determines whether prospective parents can provide the necessary elements for the adopted child. Agnecies which perform special needs adoptions usually offer classes for prospective parents to help them become aware of their strengths and limitations and to decide which kinds of disabilites they will feel capable of dealing with.

Several years ago all adoptions were closed, the records sealed and neither the adoptive parents nor the biological parents had any means of contacting the other. Now, although some families still choose a traditional closed adoption, many adotpions are open. Most biological parents choose the adoptive family; many meet the adoptive parents either by telephone or in person. Parents who receive the diagnosis prenatally may even meet the prospective adoptive parents before birth. Adoption arrangements can be made and the adoptive parents may even share in the birth experience.

Many families continue to have contact after the adoption is final. Contact may be as minimal as an occasional inquiry through a third party, usually the adoption agency. Or, it may be a relationship resembling an extended family, with the two families visiting one another in their respective homes. Adoption laws vary from state to state, yet, even in states where open adoption is not legal, the laws can sometimes be circumvented to provide all parties involved with a mutually acceptable arrangement.

Parents who consider adoption will need support and counseling for an extended time. Intensive counseling is usually necessary during the decision-making process until the parents have reached a decision they feel they can live with. Parents who relinquish will usually experience another grieving process after the papers are signed. The needs of this subgroup have, until recently, remained unknown. Parents that do relinquish have indicated that they seldom receive support from friends and relatives who assume that everything is over and it is time for them to get on with their lives. Medical professionals need to be prepared to provide follow-up with these parents and to determine whether they are receiving the support needed. If not, professionals need to be prepared to connect parents with a supportive counselor, preferably one who specializes in grief and loss.

Selected Readings

1. Self-awareness. Self-selection. and Success: A Parent Guidebook for Special Needs Adoptions, by Hamm, Wilfred, project directors; Thomas Morton; Laurie Flynn; edited by Janet Dinsmore; North American Council on Adoptable Children. Washington, D.C.

2. Clinical Practice in Adoption by Robin Winkler; Dick Brown; Margaret VanKeppel; Amy Blanchard; New York, 1988; Pergamon Press (*Not specifically related to special needs, but has chapter on relinquishing parents*).

3. Issues in Special Needs Adoption for Mental Health Practitioners, 1987, Connecticut Council on Adoption, available through the National Resource Center for Special Needs Adoption, PO Box 337, Chelsea, MI, 48118.

4. "Adopted Children with Mental Retardation: Positive Family Impact" by Laraine M. Glidden et al. Mental Retardation, 26,1988, 119-125.

5. "Adoption and Mental Retardation" by Robert G. Lewis. Pediatric Annals, 18,1989, 637- 644.

6. "Longitudinal Comparisons of Families who have Adopted Children with Mental Retardation" by Laraine M. Glidden and Jean T. Pursley. American Joumal on Mental Retardation, 94,1989, 272-277.

7. Mostly I Can Do More Things Than I Can't. Handbook developed by the Illinois Special Needs Adoption Project about planning adoptions for child with developmental disablities; 1987, Illinois Department of Children and Youth Services; available through the National Resource Center for Special Needs Adoption, PO Box 337, Chelsea, MI, 48118 for $6.00.

8. "Should We Keep Our Baby?" by Elaine Fein in Woman's Dav, 1/20/87.

9. "I Couldn't Keep My Baby" by Randy Wooldridge in Working Mother, September 1989.

10. "Psychological Disability in Women who Relinquish a Baby for Adoption" by John T. Condon and "Relinquishing Mothers" by Gordon Parker in Medical Journal of Australia, 144, 2/3/86,117-119 and 113.

11. "Developmentally Disabled Children Can Be Adopted" by Ann Coyne and Mary Ellen Brown in Child Welfare, 65,1986,189-198.

12. Ended Beginnings: Healing Childbearing Losses by Claudia Panuthos and Catherine Romeo. Warner Books, Inc., 666 Fifth Avenue, New York, NY, 10103,1984.

13. Before and After Zachariah by Fem Kupfer.

14. When Your Child is Gone: Leaming to Live Again after a Custody Decision, Disappearance, Miscarriage, or Death by Francine Toder. Ballantine Books, Random House, Inc., New York, 1986. *Includes loss due to adoption with suggestions for coping.*

Adoption Laws in New England

Adoption laws differ from state to state. Some states have open adoption systems. There are parents who have relinquished their special needs child who continue to maintain a relationship with the adoptive family and periodically visit the child.

Individuals wishing to adopt a child with special needs will have a home study performed by a public or private state-licensed child welfare agency. The home study is a process in which the adoption agency determines whether prospective parents can provide the necessary elements for the adopted child. The following agencies can provide clarification of laws in your state.

CT
Connecticut Dept. of Children and Youth Services
White Hall, Bldg 2
Undercliff Road
Meridien, CT 06450
203-238-6640

NH
New Hampshire Division for Children & Youth Servies
6 Hazen Drive
Concord, NH 03301
603-271-4701

ME
Maine Department of Human Services
State House, Station 11
221 State Street
Augusta, ME 04333
207-289-5060

MA
Massachusetts Department of Social Services
150 Causeway Street
Boston, MA 02114
617-727-0900

RI
Rhode Island Department of Children and Their Families
610 Mt. Pleasant Avenue, Bldg 7
Providence, RI 02908
401-457-4950

VT
Vermont Department of Social & Rehabilitative Services
103 S. Main Street
Waterbury, VT 05676
802-241-2131

Selected Resources on Adoption of Children with Special Needs

National Resource Center for Special Needs Adoption
Clearinghouse
Spaulding for Children
3660 Waltrous Road
Chelsea, MI 48118
313-475-8693

Family and Foster Care Adoption Program
Child Welfare League of America
440 First Street, NW
Washington, DC 20001
202-638-2925

Down Syndrome Adoption Exchange
56 Midchester Avennue
White Plains, NY 10606
914-428-1236

Adoption of Children with Spina Bifida
1955 Florida Drive
Xenia, Ohio 45385
513-372-2040

Aid to Adoption of Special Kids
AASK Midwest
1605 Holland Road; Suite A5
Maumee, Ohio 443537
419-891-0327

Project Impact
25 West Street
Boston,MA 02111
617-451-1472

Region 1 Adoption Resource Center
61 Batterymarch Street
Boston, MA 02110
617-426-8537

Mass. Adoption Exchange (MARE)
867 Boylston Street
Boston, MA 02110
617-426-8573

Rootwings Ministries, Inc.
P.O. Box 614
Barre, VT 05641
800-479-2197

Ocean State Adoption Resource Exchange
500 Prospect Street
Pawtucket, RI

Other Resources

About The Down Syndrome Adoption Exchange

The Down Syndrome Adoption Exchange (DSAE) is a private, nonprofit organization funded by charitable contributions. Established in 1976 by Janet Marchese, the Down Syndrome Adoption Exchange has facilitated the permanent adoption of over 1300 children with Down Syndrome by loving parents. A major goal of the organization is to assist the public, adoption agencies and medical personnel to better understand the facts concerning the developmental capability and value of handicapped children in general. DSAE does not charge for its services however, donations of money, talent and efforts are needed and greatly appreciated.

Down Syndrome Adoption Exchange
56 Midchester Avenue
White Plains, NY 10606
914-428-1236

OPTION 3:

Pregnancy Termination & Termination Support Services

- Barbara Thayer, M.S.
-Leslie Ciarleglio, M.S.
-Jodi Rucquoi, M.S.

Ms. Thayer is a Genetic Associate and the Associate Director of the Prenatal Diagnostic Center in Lexington, Massachusetts.

Ms. Ciarleglio is a Genetic Counselor at the University of Connecticut Health Center.

Ms. Rucquoi is a Genetic Counselor at Yale New Haven Medical Center.

All have been responsible for the development of genetic-related pregnancy termination support programs in their states.

Most women who choose to terminate a pregnancy because of a fetal disability have had to make their decision within a short period of time in order to be within the legal time limits on abortion (which varies from state to state). The decision to terminate is often made while still in a state of shock and disbelief and while grappling with medical informatin about the disability. Few people expect to be the one to receive an abnormal test result. When they do, feelings can vary greatly and include concerns about a possible misdiagnosis, sadness, anger and guilt. In addition there is often ambivalence about he decision of what to do. For those who elect pregnancy termination, there is the additional fear of the procedure, concern about the thoughts of friends and family, concern about other children and what to tell them, concern about the effect on the marraige, and fear regarding future reproductive abilities. Those who make the decision to terminate the pregnancy suffer a unique type of pregnancy loss-the loss by choice. These individuals are usually not comfortable in a general pregnancy loss or miscarriage support group. Reactions to this loss vary and may include feelings of sadness, anger, guilt, uncertainty and isolation. The opportunity to share feelings and concerns with others who have made similar choices may help to restore well-being.

Peer support programs provide a confidential setting in which to have personal contact with other individuals and couples who have been through similar experiences. Participants have found that acknowledging the physical and emotional effects of their experiences and discussing their relationships and the issues surrounding communication have helped to foster healing and acceptance.

Peer support programs have been implemented in various medical genetic centers throughout the country. Each varies in format, content and leadership. There are currently a few centers in New England that offer a termination support program-Prenatal Diagnostic Center in Lexington, Massachusetts; Harvard Community Health Plan, Boston, Massachusetts; University of Connecticut Health Center in Farmington; and Yale University in New Haven, Connecticut. Although there are differences in organization and approach, these programs share a common goal-to provide the unique opportunity for individuals and couples to garner support from peers.

AfterWords

Prenatal Diagnostic Center, Inc.
80 Hayden Avenue
Lexington, MA 02173
617-862-1171
Contact: Barbara Thayer, M.S.

AfterWords is a peer support program established in 1988 at the Prenatal Diagnostic Center (PDC). This program was developed with the assitance of Robin J.R. Blatt, Massachusetts Genetics Program, Massachusetts Department of Public Health. Initial funding was provided by the New England Regional Genetics Group (NERGG).

The purpose of the program is to provide patients with the opportunity to meet with others who made a similar choice regarding pregnancy termination after the prenatal diagnosis of a fetal disability. Patients from the PDC are informed about the group directly by physicians and counselors. Follow-up calls and a letter of invitation are also provided to those patients known to have elected termination. A brochure describing the support service is available, free of charge, for referring providers to give to patients. The support group is open to all persons who have undergone a pregnancy termination for a fetal disability. Patients do not have to be clients of the PDC in order to participate. Termination support is viewed by the PDC as an integral component of a comprehensive genetics program. There is no cost to patients for this service. Participants register for the support group over the telephone by speaking with a genetic counselor who will solicit background information as part of the intake procedure. Sessions are time-limited.

The group meets at the PDC once a week for two hours in the evening for three consecutive weeks. A new group is initiated every two months. The support groups are co-facilitated by a genetic counselor from the PDC and a social worker or therapist. The genetic counselor offers expertise in genetics and experience in working with families faced by abnormal prenatal diagnostic test results . The social worker or therapist brings experience in pregnancy loss and grief counseling and working with individuals in a group mileu. The three sessions are loosely structured. The first session deals with issues around individual experiences with prenatal diagnosis and reactions to the news as well as experience with the termination procedure. The second session focuses on communication, including how the experience has effected the couples relationship and their communication with extended family, friends , siblings, and colleagues. Issues pertinent to the provider-patient relationship are also reviewed. The third session is designed to focus on restoring health. This session involves a series of practical exercises designed to encourage the individuals to identify ways to help with coping and integrating this event into their life. Each session begins with brief didactic material however the majority of time is devoted to allowing participants discuss the issues they define as important. The sessions usually begin with individuals and couples describing their reactions to the discovery of the anomaly and their experience with the termination procedure. Common topics for discussion include the duration and intensity of grief, the differences in the reactions of males and females, communication with friends and relatives and future pregnancies. The sense of support and acceptance among the group members has been obvious to the facilitators and the clients have expressed that the groups are very productive and fill a great need. Written evaluations of the support group have revealed that 97% of particpants feel that the experience has been very helpful, 87% believe it to be somewwhat helpful, and 10% have said it was helpful. Of those responding to the questionairres, 49% of the participants believe that three sessions are adequate, and 5% believe that three sessions are too few in number. Five of the seven group series held to date have requested at least one follow-up meeting . Reorganizing the number and format of the sessions are currently being discussed as part of the ongoing project evaluation. Possible options include scheduling more sessions, having monthly or bi-monthly meetings after a set of sessions or orgqnizing reunions a few months after a specific group series has ended. Developing and implementing the AfterWords support group has been a professionally rewarding project for the staff at the Prenatal Diagnostic Center. Materials charting the development and implementation of the termination support prrogram have been compliled and are available to other centers interested in establishing a similar service program.

H.O.P.E. (Helping Other Parents Endure)

University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030
(203) 679-1501
Contact: Leslie Ciarleglio, M.S.

A pregnancy termination support program has been developed by the Divisions of Human Genetics and Maternal-Fetal medicine at the University of Connecticut Health Center in Farmington.

When a fetal anomaly is diagnosed, patients are counseled extensively about all the options available to them. For those patients who elect pregnancy termination, there is now an ongoing peer support program, called H.O.P.E., designed especially to meet the needs of this group. Originally women who terminated were referred to UConn's very active perinatal loss support group, called HEAL. This group, which is primarily made up of people who have experienced miscarraige, stillbirth, or neonatal death, was not found not to fill the specific need of the person choosing to terminate a once wanted child. Despite the fact that there were many common emotions between both groups, the distinct difference was loss by choice. The solution developed at UConn was to create a support group specifically for this group.

A brochure was developed and enclosed with an intital letter of invitation to patients who had been admitted for termination within the previous twelve months. This was later extended to include the previous three years. Brochures were also sent to most obstetrical office practices in Connecticut. The first H.O.P.E. meeting was primarily a brainstorming session with parents.

The H.O.P.E. group is structured to meet once a month. Participants can drop in or out at any time. There is no charge for this service. parents are welcome to attend individually or as couples. Other family members or friends are welcome to attend, however, the partipication of children is not encouraged. Meetings are co-facilitated by genetic counselors and/or nurses. The role of the facilitator is to assist in the introductions and to initiate conversation, but not to lead the group. The discussions are by and for parents. Each session is scheduled for 1- 2 hours, although parents frequently continue their discussions past the predetermined time. A team of professionals, including a medical geneticist, a perinatologist, a chaplain and a psychotherapist are available to all participants for private consultations.

The availability of the termination support group is usually introduced to patients as part of counseling about second trimester genetics termination of pregnancy. On admission, patients are given a brochure describing H.O.P.E. and an initial letter of invitation to attend the program. Ten days prior to each monthly meeting, these individuals receive a mailing inviting them to attend. Monthly letters of invitation continue until otherwise requested. If a substantial period of time passess and the individual has not attended a meeting, a final "good-bye" letter is sent to the patient.

The reponse to this program has been extremely positive and clealry filling a need. At each meeting there is a wealth of understanding and compassion amonngst the group. A telephone list has been developed with the goal fo establishing a formal network so that H.O.P.E. group parents are available to families who desire support while in the midst of dealing with their loss. A small lending library has also been developed.

As a facilitator, I find the H.O.P.E. group to be an invaluable experience - not only in the guidance the group provides, but also in the motivation parents inspire.

Termination Support

Yale-New Haven Medical Center
Department of Human Genetics
P.O. Box 3333
New Haven, CT 06510-8003
203 - 785-2663
Contact: Jodi Rucquoi, M.S.

In the early 1980's women who chose to terminate their pregnancy following amniocentesis at Yale-New Haven Medical Center were questioned in order to assess the effect on their lives. A questionairre was developed to provide information about the experience of pregnancy termination and to learn what factors influenced the experience and how the experience might be improved.

After a review of the data, the same individuals were invited to a meeting to discuss the issues that were raised. The result of these efforts led to the development of a booklet that is provided to all patients upon receipt of an abnormal prenatal diagnostic test result. The booklet discusses aspsects of decision making, the termination process, post-delivery options, suggestions for talking with other children, family and friends about the experience and it addresses some of the psychological sequalae associated with pregnancy termination.

A very important part of our protocol is the follow up that is offered. We have found that a variety of options gives women the opportunity to choose a more comfortable way of dealing with this epxerience in the weeks and months after the termination. While group support sessions may be the choice of some individuals, others prefer private meetings with a counselor or elephone conversations with another woman or couple. There is now a well- developed network of individuals who are available to talk with others. Our experience shows that some women choose to reach out for help only after several months have gone by, while others want contact sooneer. In some situations, years have passed and some event may trigger a need to reach out.

Two satellite clinics (Bridgeport and Norwalk Hosptials) have combined their resources and now offer group counseling under the guidance of genetic counselors Sharon Suntag, JoAnn Inserra, and Cindy Malin. Their first group is coming to closure after one year. For the first month, one couple and four mothers met weekly and then monthly for the remainder of the year. The second group started by the couneslors consisted of two couples and one mother an ran for one month. The counselors feel that at least three individuals or couples are need to begin a new group. Groups are now organized on an ongoing basis.

It is importnat to recognize that the fetal loss issue is superimposed upon a kaleidoscope, or substrate of issues. Previous loss, previous birth, length of gestation, quality of marital relationship, and demographic characteristics can have an impact on the way the experience is percieved and handled. As part of the counseling it is important to include a discussion of issues originating in the family, such as how the families express sadness, caring, love and fear and how each individual experiences feelings of well-being, safety, and self-esteem. Perhaps one of the most important items in the Yale-New Haven pre-termination protocol is the oportunity to veiw the fetus, to say "hello" before beginning to say "goodbye," what. The acknowledge-ment and acceptance of the fetus by both parents is often the first step towards recovery. This becomes difficult when the termination procedure precludes veiwing an intact fetus. There are other ways to help women establish the reality of the fetus; one is writing a letter and expressing ones thoughts and feelings.

We continue to seek ways to improve our pregnancy termination service. With more women choosing early diagnostic procedures, it remains to be seen whether or not the grieving process will be shortened or perhaps lessend by the earlier termination. Our experience with second trimester abortions has taught us that preparing women and their partners to deal with their grief is a very important part of patient care. ◆

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New England Regional Genetics Group (NERGG)

NERGG CoordiNotes

There has been discussion for sometime about regionalizing ***The Genetic Resource*** *and I am pleased to see this first regional issue finally become a reality. We hope that readers who are new as a result of expansion of this fine publication will find the content as useful and informative as readers in Massachusetts have done in the past.*

It was with regret that I lost the services of my assistant, Peggy Elder, when I moved the NERGG office to Maine. I am pleased to have found an able new assistant Virginia Riley, who is also working as the NERGG Data Coordinator, and whose acquaintance some of you have made in your interactions with the NERGG office. As you read through the information about NERGG, I hope that it will attract your interest. If you would like to be placed on the NERGG mailing list, to become involved in one of the operating committees, or to receive more information about any aspect of NERGG, please contact Virginia or me in the NERGG office and we shall be happy to assist you.

A. Merrill Henderson, M.S.,
NERGG Coordinator

For More Information

New England Regional Genetics Group
(NERGG)
36 Ledge Lane
PO Box 682
Gorham, ME 04038-0682
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ATTN: A. Merrill Henderson, M.S.
NERGG Coordinator

New England Regional Genetics Group (NERGG)

The New England Regional Genetics Group is a consortium of genetic service providers, public health planners, consumer groups, and federal and state maternal and child health personnel in New England (Region 1). NERGG's purpose is to promote the availability of high quality human genetic services and to encourage activities in genetic education throughout New England. To this end NERGG supports numerous projects where regional activities or perspectives will enhance progress in the field. NERGG assists in communication among service centers, state programs, and public interests, and joins with the Council of Regional Networks (CORN) in national planning. Particular concern is given to data collection, communication, coordination, utilization of new technologies, quality assurance and ethical issues arising in the field. NERGG welcomes contact with persons or groups who share its interests.

History of NERGG

In 1977 a project grant was awarded to the Developmental Evaluation Center at Children's Hospital by DHEW, Public Health Service, Division of Maternal and Child Health. This grant led to a feasibility study for regionalization of genetic services and then to a conference with participants from the major centers for genetic service programs, state public health agencies and consumer groups. The conference formed the New England Regional Genetics Group, whose mission was to carry out regional genetic service planning in New England.

Purpose of NERGG

NERGG's purpose is to provide a forum for the discussion of region-wide concerns regarding the provision of optimal services in medical genetics, to promote the availability of high quality human genetic services, to ensure that providers, consumers and state health department personnel have the opportunity to discuss issues of mutual interest, and to encourage active genetic education throughout New England. To this end NERGG supports several region-wide projects.

Organization

Ten operating committees carry out the central business of NERGG. The Steering Committee, consisting of the NERGG Directors, a representative service provider, public health planner and consumer from each state, and the chairs of the operating commmitees, meets three times a year to review projects and to discuss NERGG's program and actions. The Annual Meeting, held in early December, brings together the Steering Committee members with service providers, public health planners, consumer groups, and others with an interest in genetic services in the Region.

Grants and Awards

Each year NERGG dedicates a portion of its funding to the accomplishment of special projects to further its goals in the region. Project proposals are solicited and reviewed during the early part of each calendar year by the Grant Review Committee. Between six and ten proposals are funded yearly.

Membership

Any individual who has demonstrated interest in the mission of NERGG and has an affiliation with an organization having a direct relationship to genetics in the New England Region can become a member of NERGG. The major examples of such organizations are 1) facilities providing genetic services, such as diagnosis, intervention and counseling; 2) elements within the Department of Health and other state government agencies where genetic programs are based; 3) established consumer organizations that have significant involvement int he areas of hereditary conditions and/or birth defects; 4) special city, state, or regional projects, either privately or publicly funded, that focus on the issues of related disorders such as sickle cell disease, hemophilia, Huntington disease, etc.; 5) research or educational facilities with significant medical genetic concerns and with a role in public health planning; and 6) commercial providers of medical genetic products and services. All members are eligible to receive NERGG mailings, to submit proposals for NERGG projects, to vote for officers and to vote on the Bylaws and Organizational Guidelines, and to attend the Annual Meeting.

New England Regional Genetics Group (NERGG) Steering Committee 1991

CO-DIRECTORS

Allen C. Crocker, M.D.
Lewis B. Holmes, M.D.
Marsha T. Lanes, M.S.

PAST CO-DIRECTOR

Stacey T. Kacoyanis, M.S.

COMMITTEE CHAIRS

Consumer Concerns Committee
Betsy Anderson

Data Committee
Solveig Pflueger , M.D.

Education Committee
Paula K. Haddow, M.A.T.

Grant Review Committee
Laurent Beauregard, Ph.D.

Outreach Committee
Marsha T. Lanes, M.S.

Prenatal Diagnosis Committee
Wayne A. Miller, M.D.

Prevalence Committee
Lewis B. Holmes, M.D.

Screening Committee
Margretta Seashore, M.D.

Finance Committee
Robert M. Greenstein, M.D.

Quality Assurance Committee
James E. Haddow, M.D.

STATE REPRESENTATIVES

Connecticut
Leslie Ciarleglio, M.S., Service Provider
Jadwiga Goclowski, Ph.D., R.N., Health Planner
Victoria Odesina, R.N., Consumer

Maine
Laurent Beauregard, Ph.D., Service Provider
Zsolt Koppanyi, M.D., M.P.H., Health Planner

Massachusetts
Marvin Natowicz, M.D., Ph.D., Service Provider
Marsha T. Lanes, M.S., Health Planner

New Hampshire
John Moeschler, M.D., Service Provider
Jane Hybsch, Health Planner
Jamie Stevenson, Consumer

Rhode Island
Anne Richardson, Service Provider
Peter Simon M.D., M.P.H., Health Planner
Mary Leyden, Consumer

Vermont
Carol Walters, Ph.D., Service Provider
Ellen Thompson, M.S., R.D., Health Planner Hope
Charkins-Drazin, Consumer

1991 NERGG Meetings 1991

Meeting	Date & Time	Place
➤**NERGG Steering Committee**	February 11 10:00 a.m. - 3:00 p.m.	Bulfinch Conference Room Mass General Hospital
	June 17 10 a.m. - 3 p.m.	Bulfinch Conference Room Mass General Hospital
	September 9	Bulfinch Conference Room
	10 a.m. - 3 p.m.	Mass General Hospital
➤**Hemoglobinopathy Task Force**	February 1 1p.m. - 4 p.m.	Publick House Sturbridge, MA
	April 19 1p.m. - 4 p.m.	Mass. State Lab. Institute Jamaica Plain, MA
	June 21 1p.m. - 4 p.m.	(Site to be Announced)
	August 23 1p.m. - 4 p.m.	(Site to be Announced)
➤**School Nurse Curriculum Committee**	April 19 10:00 a.m. - 12 noon	Mass. State Lab. Institute Jamaica Plain, MA
➤**Prenatal Diagnosis Committee**	April 8 & 9 Sturbridge, MA	Publick House
	December 11 1:30 p.m. - 4:30 p.m.	New England Center Durham, N.H.
➤**New England Myelodysplasia Association(NEMA)**	March 1 10:00 a.m. - 4:00 p.m.	UMass Medical Center Worcester, MA
	June 7 10:00 a.m. - 4:00 p.m.	UMass Medical Center Worcester, MA
	September 13 10:00 a.m. - 4:00 p.m.	UMass Medical Center Worcester, MA
➤**New England Regional Peer Support Conference**	April 12 Manchester, N.H.	Manchester Country Club
➤**NE/Eastern Canada Clinical Genetics Conference**	May 30 - June 1 Burlington, VT	University of Vermont
➤**Second New England Regional Sickle Cell Conference**	September 20 Hartford, CT	(Site to be Announced)
➤**Region 1 National Society of Genetic Counselors**	December 11 Durham, N.H.	New England Center
➤**NERGG Annual Meeting**	December 11 & 12 Durham, N.H.	New England Center

To be placed on the mailing list for notification of any of the above meetings, or for more information about them, please contact the NERGG office.

Tel: 207-839-5324/Fax: 207-839-8637

1991 General Genetics Meetings 1991

Meeting	Date	Contact
➤**The Human Genome Project: New Tools for Tomorrow's Health Research** National Institutes of Health	January 14	Sandy O'Connor 301-402-0911
➤**Molecular Genetic Techniques in the Diagnosis of Genetic Diseases** Baylor College of Medicine Houston, TX	February 28 - March 2	Edward R.B. McCabe, M.D., Ph.D. 713-798-5820
➤**Legal & Ethical Issues Raised by The Human Genome Project** The Houstonian Hotel Houston, TX	March 7-9	Cathy Tanenbaum 713-749-3872
➤**Youth in Preparation for Independence** Educational & Networking sessions for youth with disabilities Eliot Church Newton, MA	Ongoing Sessions	Maureen Gallagher 617-727-7440
➤**The Human Genome Project 1st Massachusetts Public Forum** Federal Reserve Bank of Boston Boston, MA	April 8	Robin J.R. Blatt 617-727-5121
➤**A Conference on Biotechnology for the Diagnosis of Genetic Disease** Arlington, VA	April 18-20	Susann Wilkinson 202-687-5391
➤**New England Regional Peer Support Conference** Manchester Country Club Bedford, NH	April 19	Martha Jean Madison 603-942-5540
➤**Human Teratogens: Environmental Factors Which Cause Birth Defects** Ritz-Carlton Hotel Boston, MA	April 29 - May 1	Harvard Medical School Dept. of Cont. Education 617-432-1525
➤**Mental Retardation and Developmental Disabilties: Diagnosis, Therapy, and Prevention** Omni Parker House Boston, MA	May 8-10	Harvard Medical School Dept. of Cont. Education 617-432-1525
➤**AFP Course** Foundation for Blood Research Scarborough ME	June 3-5	Polly Haddow 207-883-4131

NERGG Committees

***Ad Hoc* Subcommittee on Bone Marrow Transplantation and Other Treatments: Allen C. Crocker, M.D., Chair** • *This is a subcommittee of the Screening Committee. The purpose of this committee is to monitor the progress of bone marrow transplantation and other new treatments for genetic diseases.*

Consumer Concerns Committee: Betsy Anderson, Chair • *The purpose of this committee is to act as a voice for the interests of self-help groups and to monitor activities of other committees and of NERGG projects from the viewpoint of the consumer.*

Cytogenetics Subcommittee: Wayne A. Miller, M.D., Chair • *This is a subcommittee of the Prenatal Diagnosis Committee. Its purpose is to provide a forum for communication among cytogenetic laboratories in the region in order to improve the quality of cytogenetic services in the region.*

Data Committee: Solveig Pflueger , M.D., Chair • *The purpose of this committee is to bring together representatives from prenatal, newborn, and general genetics to monitor GenSeM (Genetic Service Monitoring), the NERGG data collection project.*

DNA Subcommittee: Katherine Klinger, Ph.D., Chair • *This is a subcommittee of the Prenatal Diagnosis Committee. Its purpose is to improve communication among DNA laboratories in the region and to monitor the status of new DNA tests.*

Education Committee: Paula K. Haddow, M.A.T., Chair • *The purpose of this committee is to assess and devise plans to address needs for genetic education throughout New England.*

Grant Review Committee: Laurent Beauregard, Ph.D., Chair • *The purpose of this committee is to draft NERGG program priorities for presentation to the NERGG Steering Committee and to review and make recommendations about proposals for NERGG special projects.*

Membership Committee • *In the organizational stage.*

New England Myelodysplasia Association (NEMA): Robin Leger, R.N., M.S., Chair; Kathleen Kalell, R.N., Coordinator • *This is a subcommittee of the Consumer Concerns Committee. Its purpose is to monitor and improve the care of individuals with spina bifida and their families in the region.*

Outreach Committee: Marsha T. Lanes, M.S., Chair • *The purpose of this committee is to identify underserved areas and populations and propose ways in which NERGG can address these issues.*

Prenatal Diagnosis Committee: Wayne A. Miller, M.D., Chair • *The purpose of this committee is to represent the activities and concerns of the prenatal diagnostic centers in New England. It includes subcommittees on cytogenetics and clinical applications of DNA analysis. and monitors laboratory activity. It also sponsors one continuing education seminar annually.*

Prevalence Committee: Lewis B. Holmes, M.D., Chair • *The purpose of this committee is to develop methods for gathering data on incidence of birth defects.*

Screening Committee: Margretta Seashore, M.D., Chair • *The purpose of this committee is to promote current newborn screening programs, to suggest policies for follow-up, and to investigate the feasibility of new tests.*

The Task Force on Screening for Sickle Cell Anemia and Other Hemoglobinopathies: Steven Weisman, M.D., Emily Lazar, M.S., Co-Chairs • *This is a subcommittee of the Screening Committee. Its purpose is to monitor the progress of screening programs for sickle cell and other hemoglobinopathies and to coordinator and improve follow-up care for affected individuals and their families.*

Finance Committee: Robert M. Greenstein, M.D. • *The purpose of this committee is to survey reimbursement practices for genetic services and to maintain contact with major insurance carriers.*

Quality Assurance Committee: James E. Haddow, M.D., Chair • *The purpose of this committee is to address quality assurance issues with emphasis on prenatal screening markers.*

NERGG Special Projects

1991

Genetic Services Monitoring (GenSeM)

Principal Investigator: Glenn E. Palomaki, B.S.

In 1986, NERGG launched into collection of data on genetic services. The first report, prepared for the calendar year 1988 with nine centers participating, documented 10,065 services on 5,167 patients who completed 5,686 visits. By the end of 1989, most small genetic centers in the New England region were contributing to the data collection effort. During 1991 and the ensuing years, the large genetic centers in New England will be encouraged to join the data project and data will also be collected from newborn screening programs. GenSeM will provide a framework for the collection, verification, analysis and reporting of genetic data. Systems will be developed for documenting **pregnancy demographics** by state and county, including the number of live births, stratified by location, maternal age, and maternal race; documenting genetic services delivered by center, state, and, if possible, county related to MSAFP testing, amniocentesis, and counseling; and integrating the existing NERGG data collection effort aimed at documenting fetal disorders indentified by MSAFP screening. In addition, systems will be developed to integrate the existing information from the **newborn screening** services, stratified by state, and if possible, by county, including newborn disorders identified. GenSeM will also develop systems for documenting **general population demographics**, such as sex ratio, race and age distribution by state and county; documenting genetic services delivered by center, state, and, if possible, county for diagnostic and counseling services; and documenting the number and types of diagnoses made as a result of genetic services.

New England System of Collaborative Clinical Genetics: Developing Methods to Collect and Exchange Information on Low Incidence Conditions

Principal Investigator: Barbara Pober, M.D., M.P.H.

The purpose of this project is to develop a system through which professionals and parents can exchange several different types of information on low incidence conditions. Williams syndrome, an uncommon congenital multi-system disorder for which there is currently no diagnostic test, has been chosen as the model for developing the system. The goals of this project are to 1) advance knowledge concerning uncommon recognizable syndromes by developing diagnostic and management guidelines to serve as clinical education tools for the condition, identifying researchers interested in the condition to generate research hypotheses and facilitate collaborative research, and developing a regional computerized data base of researchers; 2) facilitate access to support services in New England by enlisting support from local family support groups and developing a regional computer-based network of family supports; and 3) improve the quality of clinical care to patients with low incidence conditions through dissemination of materials developed from the project to assure that comparable and high standards of care can be offered to all patients with recognizable uncommon conditions.

Prenatal Screening for Fetal Down Syndrome Using the New Biochemical Markers

Principal Investigators: James E. Haddow, M.D., Jacob Canick, Ph.D., Wayne A. Miller, M.D.

This project will integrate quality assurance protocols into the existing External Quality Control Scheme and prospectively collect data necessary to better define the process for screening a general pregnant population with two new biochemical markers, unconjugated estriol and human chorionic gonadotropin, in combination with maternal serum alpha-fetoprotein (MSAFP) and maternal age.

Study of Prevalence of Major Birth Defects in New England

Principal Investigator: Lewis B. Holmes, M.D.

This project is designed to select several common birth defects and compare their reported prevalence for one year in the states of Connecticut, Maine, Massachusetts, and Rhode Island. One of the innovations that has made it possible to compare prevalence data from one state to another is the introduction of computerized hospital discharge diagnoses for use in reporting on birth certificates. The effectiveness of this approach will be assessed by comparison of its findings with those of the active birth defect surveillance program in place at the Brigham and Women's Hospital in Boston. The findings of this study will be relevant to the addition of computer-based discharge diagnoses to birth certificates in other sections of the country. Another aspect of this project is to study the impact of elective terminations of pregnancies on the incidence of common birth defects following prenatal detection of malformations. This study will be conducted via a cooperative study with all the prenatal diagnosis centers in New England.

Regionalization of The Genetic Resource

Principal Investigators: Robin J. R. Blatt, M.P.H., Wayne A. Miller, M.D., Paula K. Haddow, M.A.T.

The purpose of this project is to provide information about developments in human genetics to New England's health care providers, consumers and educators via **The Genetic Resource**, a semiannual publication distributed to health professionals and consumers interested in developments in human genetics. Founded in 1983, **The Genetic Resource** was established in Massachusetts in order to keep practitioners, public health planners, and consumers up-to-date on new research, clinical information and the accompanying social, legal and ethical issues in human genetics. This project is designed to broaden the distribution, develop a regional editorial board and to establish a regional format for continued issues. In addition, the feasibility of continuing the publication through subsrciptions, NERGG membership dues, and advertising will be assessed.

Development of a Health Care Program for Adults with Inborn Errors of Metabolism

Principal Investigator: Mark S. Korson, M.D.

This project involves the assessment of the current status of health care for adults with inborn errors of amino and organic acid metabolism and galctosemia and and identification and description of this population. It will be done through both a clinical survey and a patient family survey. Upon completion of the surveys, a model program for the clinical management of adult patients with inborn errors of metabolism will be developed. This can also serve as a prototype for other genetic and metabolic diseases.

School Nurse as Facilitator of Medical and Educational Management of Children with Sickle Cell Disease in the School Setting: A Training Manual

Principal Investigator: Paula K. Haddow M.A.T.

The overall purpose of this project is to help children with sickle cell disease to maintain good academic achievement. The objective is to train school nurses to 1) understand the medical management of sickle cell disease to the degree that they can coordinate with the specialty care provider and manage medical problems in the school setting themselves and know when and where to refer the child for management, 2) understand the nature of the disease to the extent that they can help the teachers understand special educational needs of children with the disorder, such as home tutoring, resource room help, etc., and 3) understand the special needs of these children to the extent that the nurses can help educate other students.

Accepted NERGG Projects

(Alternative Funding Sources Being Sought)

Determination of the Frequency of Heterozygosity for Tay-Sachs Disease in French-Canadians in New England

Principal Investigators: Gale B. Gardiner, M.S., Marvin Natowicz, M.D., Ph.D.

The primary purpose of this study is to determine the frequency of Tay-Sachs disease in persons of French-Canadian background in New England. Data from this prospective study will be disseminated to primary care providers and genetic centers throughout the Region. If the data indicate an increased gene frequency in this population then a secondary purpose of this study would include education of the French-Canadian community and health care providers about this risk.

Genetic Laboratory Data Base

Principal Investigator: Edward M. Kloza, M.S.

This project will develop and maintain a computerized data base containing accurate, up-to-date, and complete information on genetic laboratory testing. The information in this data base will be made available to genetic professionals who wish to compare test methodologies, turn around time, patient eligibility criteria, cost, shipping and handling requirements, etc., before ordering genetic tests. This data base will be an unbiased source of information that does not endorse any laboratory, methodology, or protocol.

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News about NERRGniks

Edward M. Kloza, M.S., Director of Public Relations at the Foundation for Blood Research, has been elected President of the National Society of Genetic Counselors (NSGC). He will assume the post in October 1991 at the International Congress of Human Genetics in Washington, D.C.

Marsha T. Lanes, M.S., Director of the Massachusetts Genetics Program, Mass-achusetts Department of Public Health, has been elected to the office of NERGG Co-Director for a three-year term that began in December 1990.

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Awards

Robert M. Greenstein, M.D., School of Medicine of the University of Connecticut, recently received a Special Project of Regional and National Significance (SPRANS) Grant desinged to improve access and utilization of clinical genetic services for ethnic minorities in The Greater Hartford Area, especially for Latinos/Puerto Ricans. The project will be coordinated by Ms. Evelyn Gonzalez, M.S. One of the goals of this project is to develop and implement an in-service training package (ISTP) including lectures, videotapes, and printed materials which are culturally specific and sensitive for the Latino/Puerto Rican population. This package will be focused on the providers of primary care prenatal services as well as private practice OBs. The ISTP will serve as methodology to be replicated at other sites in Connecticut,the region and nationally. Educational materials will be developed about genetic services. The purpose of the project is to improve the access and utilization of genetic services by the Latino/Puerto community, thus improving pregnancy outcomes and reducing infant mortality.

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State Genetics Program Reports

Reports on 1990 activities prepared for the NERGG Annual Meeting.

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Connecticut Genetics Program

The Connecticut Genetics Program strives to 1) decrease infant mortality and morbidity due to genetic disease, 2) identify individuals who would benefit from a genetic evaluation and make apropriate referrals for clinical care, 3) increase professional and public awareness of genetics, and 4) carry out legislative mandates with respect to screening and surveillance of genetic disease. To attain these goals, the Connecticut Department of Health Services (DOHS) contracts with Yale Department of Human Genetics and University of Connecticut Department of Pediatrics to provide genetic clinical services at various field locations around the state. the Connecticut Department of Health Services funding for the genetics program has not increased in the past three years. Within the state's genetics program, there are six (6) components: Clinical Genetics, Pregnancy Risk Line, Maternal PKU, Community Trait Screening, Newborn Screening and Genetic Education. ■

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Massachusetts Genetics Program

The Massachusetts Genetics Program (MGP) is based within the Division for Children with Special Health Care Needs, Bureau of Parent, Child and Adolescent Health, Massachusetts Department of Public Health. The Genetics Program staff are Marsha Lanes, M.S., Director; Robin J.R. Blatt, M.P.H., Education Coordinator; Elizabeth Bingay, M.S., Congenital Anomaly Surveillance Coordinator. The mission of the MGP is to facilitate access to genetic screening, counseling, diagnostic and support services and information about the prevention of inherited conditions and birth defects for all residents of the Commonwealth. The objectives are to 1) develop and disseminate genetics educational materials and conduct educational programs for health care profesionals, 2) provide information and referral to the public about genetic screening, counseling, diagnostic and support services, 3) work with professional educators to promote human genetics education in schools 4) develop policy and standards for genetic testing laboratories, and 5) provide technical assistance and training to other Department of Public Health programs, professional and consumer organziations and public and private agencies. During the past year the MGP accomplished the following activities, 1) publication of **The Genetic Resource** (Volume 10, Number 2) addressing issues related to perinatal and pediatric AIDS and coordination of the transition of **The Genetic Resource** to a regionally focused publication, 2) revision of consumer brochures on genetic counseling and maternal serum alpha-fetoprotein (MSAFP) screening, 3) publication of an informational packet on prenatal genetic tests in eight languages for low literacy populations in English, Chinese, Laotian, Khmer, French, Spanish, Portuguese and Vietnamese, 4) coordination of a symposium, "*Genetics, Biotechnology and Public Health,*" sponsored by the Biotechnology Center of Excellence, the Massachusetts Genetics Program, Brigham and Women's Hospital and the Massachusetts Biotechnology Council, 5) training of 190 secondary school teachers about human genetics at three two-day conferences, 6) completion of two new units for the MGP's curriculum supplement "*Human Genetics: A Practical Teaching Guide*" on recombinant DNA and human genetics applications of recombinant DNA technology, 7) completion of a descriptive list of audiovisual materials in our lending library for teachers that includes a content summary, recommended grade level, year of production, length and limitations for each resource avialable for loan, 8) development of a report on completeness of congenital anomaly reporting to the state-mandated High Risk Infant Identification System, 9) transition of newborn sickle cell disease screening from the Boston Sickle Cell Center to the State Laboratory Institute, Massachusetts Department of Public Health; maintenance of sickle cell disease and trait follow-up program through fee-for-service for newborn screening following completion of a SPRANS grant, and 10) implementation of the federally funded Southeast Asian Birthing and Infancy Project (SABAI) to reduce barriers and increase access to prenatal, genetics and other maternal and child health services among Southeast Asian refugees in Lowell; training of bilingual/bicultural community health advocates about genetics, thalassemia, prenatal diagnosis and newborn screening. ■

The Maine Genetics program is managed by the Maine Department of Human Services, Bureau of Health, Division of Maternal and Child Health (DMCH). Newborn Screening Program activities are conducted directly by DMCH staff. Comprehensive genetic services are partially funded via state grant funds to the Southern Maine Genetic Service at the Foundation for Blood Research in Scarborough and the Genetics Program at Eastern Maine Medical Center in Bangor. In fiscal year 1990, genetic services were provided in seven locations across the state. Approximately 625 new patients were seen and total patient visits reached 1,098. Laboratory studies performed by the EMMC Cytogenetics Lab increased over the previous year by about 14%. MSAFP screening increased by 6% over the previous year's experience. A total of 12,341 women, or approximately 70% of total pregnancies, received MSAFP screening through the Foundation for Blood Research. The Newborn Screening Program screened 16,873 newborns during calendar year 1989. Three infants were detected with hypothyroidism, three with classical PKU, and three with hyperphenylalaninemia. ■

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New Hampshire Genetics Program

Dartmouth Hitchcock Medical Center (DHMC) and the Bureau of Special Medical Services (BSMS) continue to work together to provide New Hampshire residents with quality genetic services. Clinical services include inpatient and outpatient consultations, regional clinics, and prenatal diagnosis services. A new regional clinic site in Nashua has been established expanding the number of clinic sites to 11. In 1990, 275 outpatient and regional genetic clinic visits occurred. Of these 171 were new patients and 104 were return visits. Inpatient consults totaled 75. There were 920 prenatal diagnosis visits. The Collaborative Services Project grant provides developmental screening and follow-up services for children with a known diagnosis who are 6 years of age or younger, as part of the genetic clinic visit. 17,391 newborn screening samples were processed. Targeted newborn screening for sickle cell disease began in October 1990. The Molecular Genetic Laboratory at DHMC examined a total of 75 cases including lymphomas/leukemias (24), cystic fibrosis carrier detection and prenatal diagnosis (35), and Duchenne/Becker Muscular Dystrophy carrier detection (10). The cytogenetics laboratory at DHMC analyzed 158 serum samples, 85 bone marrows, 30 skin biopsies, 607 amniotic fluids. 39 Fragile-X analyses and 23 mosaic checks were also performed. Chorionic villus sampling (CVS) and Percutaneous Umbilical Blood Sampling (PUBS) procedures are now being offered through the Prenatal Diagnosis Program. Parent/professional collaboration has expanded. Collaboration with the Upper Valley Support Group has established the Parent to Parent Network of New Hampshire. The Bureau of Special Medical Services held a parent network leader training session and a parent policy group has been established to review BSMS program policies. ■

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Rhode Island Genetics Program

Rhode Island continues to provide genetic services on a statewide basis with much of the emphasis focusing on newborn metabolic and hemoglobinopathy training. In May, 1990, the laboratory analysis for the hemoglobinopathy screening program was transferred from the Boston Sickle Cell Center to the Regional Newborn Screening Laboratory at the Massachusetts State Laboratory Institute. In addition to case detection, a half time sickle cell nurse coordinator has been hired at Rhode Island Hospital to ensure case management, care coordination and parental education for these families, and for other families with identified hemoglobinopathies. A statewide genetic conference entitled,"Genetics in the Primary Care Setting" was offered this fall in Newport. Approximately 120 pediatric and prenatal nurses, WIC nutritionists, dietitians and physicians attended the conference which focused on trait counseling, the hemoglobinopathies, AFP and AFP PLUS screening, general nutritional concerns, etc. Additionally the program is finalizing the development of some multilingual low literacy materials on genetics, Hemoglobin E and thalassemia; and a Rhode Island Hospital Comprehensive Sickle Cell clinic brochure. The newborn screening program is currently self supporting by charging a fee of $25.00 per live birth to each hospital and returning that money into a restricted account which can only be used to support program costs. ■

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Vermont Genetics Program

The Vermont Regional Genetics Center (VRGC) was again able to increase its activities, despite less than 1% increase in funding from the Department of Health. **Direct patient services** increased over 16%; **outreach clinics** were continued. Other clinic sites in New York were suspended due to lack of funding. VRGC staff were involved in the design and initiation of the Handicapped Children's Services' new Metabolic Clinic which offers comprehensive evaluation and follow-up for individuals with inborn errors of metabolism and related conditions. Calls to the **Pregnancy Risk Information Service** increased over 15%, and this service now has contact with almost 20% of all Vermont pregnancies. The circulation of its bimonthly newsletter continues to expand. Participation in MSAFP screening remains stable at 45% of Vermont pregnancies; almost 25% of the total screening samples come from the upper three counties of New York. In its first 1-1/2 years as part of the New England program (Vermont joined the New England Regional Newborn Screening Program in July 1989) program, the Newborn Screening Program has documented screening of over 99% of infants born in the state, including 80% of the 132 recorded home births. Targeted screening for sickle cell disease has identified two individuals with SC trait (one S and one C) among the 16 infants tested (36 black births recorded). Direct billing for screening to hospitals, physicians and patients (home births) has produced a 99% collection rate. ■

Previous NERGG Accomplishments

- Increased reach from a membership of 31 at the founding meeting in 1978 to a mailing list of over 300 in 1990 representing all comprehensive genetic centers and state maternal and child health programs in the Region, other regional programs, consumer groups, and federal agency personnel.
- Assistance provided to state health departments to maintain genetic services in the face of an adverse fiscal environment. All six of the New England states have retained public support for genetic services .
- Introduced genetic curricula to primary and secondary school grades in many schools through education of teachers by NERGG's Education Committee. Continuing education modules for high school teachers in genetics through regional workshops and the introduction of Chances' Choices, a new supplementary curriculum on human genetics, have now spread nationwide.
- Increased awareness in state health departments of quality control issues in genetic testing through advisory notices and letters to professional journals on issues such as alpha-fetoprotein (AFP) screening, chorionic villus sampling, cytogenetic quality assurance, and screening for cystic fibrosis.
- Establishment of an external laboratory quality assurance scheme for maternal serum AFP (MSAFP), now expanded to include amniotic fluid AFP and new screening markers for Down syndrome. This program has become international in scope.

- Development of a lively partnership among eight centers in Connecticut, Massachusetts, Maine, Rhode Island and Vermont to produce improved risk tables for Down syndrome using MSAFP screening data and to study and establish the feasibility of screening prenatally for Down syndrome using MSAFP (Am J Obstet Gynecol, 160:575-581, March, 1989).
- Collection of 8 years' data on the utilization of amniocentesis in New England (1978-1985) and development of a minimum data set (MDS) beginning in 1986 to monitor the provision of all genetic services in the Region. The MDS report for 1988, the most recent year completed, documented services provided to over 5,000 patients.
- Establishment of a network of professionals experienced in pathology and genetics to respond to queries from practitioners and patients concerning malformed or teratogen-exposed fetuses. Started as a regional project, this service has expanded to include centers in the United Kingdom, Europe, and South America and has added computer software to provide free syndrome searches.
- Education of genetic service providers about the third party reimbursement system and of third party payers about genetics through conferences and training sessions in order to improve the funding of genetic services.
- Promotion of genetic support groups and their activities, including development of a parent support group model for families of children with fatal inherited degenerative diseases and formation of a new group based on the model, partial funding a regional meeting that led to the organization of the Connecticut Chapter of the Down Syndrome Congress, and establishment of the New England Fragile-X Parents' Organziation.
- Founding of a periodical survey of genetic articles in professional and lay publications. *The Genetic Digest* was an outgrowth of efforts to provide genetic education for high school teachers. *The Genetic Digest* is now self-supporting through subscriptions and is distributed to teachers, health professionals, and others with an interest in genetics throughout the United States and in several foreign countries.
- Production of the sound track for a video on sickle cell performed as a "rap." Young Nation, the group that produced the piece, has received exposure throughout the Region and nationally.
- Completion of a study of attitudes toward DNA testing on the part of families affected with cystic fibrosis. This study involved 12 cystic fibrosis centers in New England. Results provide information valuable for serving families considering DNA testing for CF as well as for other conditions.
- Introduction of a genetic risk screening tool into family planning clinics in Connecticut, Maine, New Hampshire, and Vermont.
- Sponsorship of major regional conferences on sickle cell anemia (September 1989) and genetic and newborn screening (April 1990) as well as numerous other conferences to educate residents of the Region about various aspects of human genetics.
- Production of two films portraying parents' experiences with their children affected by Down syndrome and spina bifida.
- Organization and co-sponsorship of clergy conferences designed to introduce members of varying religious faiths about the ethical issues inherent in genetic decision making.

NERGG MAILBAG

Prenatal Tests: Multilingual Educational Booklets
Prenatal Tests describes MSAFP screening, ultrasound, amniocentesis, pregnancy options and genetic counseling. Written for low literacy populations and available in Chinese, English, French, Khmer (Cambodian), Laotian, Portugeuse, Spanish and Vietnamese. (Haitian-Creole language version is in process of development). English translation accompanies major headings in order to assist the provider in counseling. Funding for these booklets was provided by NERGG (1989-1990) and the Massachusetts Genetics Program. Principal Investigators: Robin J. R. Blatt and Paula K. Haddow. Information may be photocopied in whole or part. Booklets can also be obtained for a nominal fee. New England Regional Genetics Group, 36 Ledge Lane, P.O. Box 682, Gorham, ME 04038-0682, 207-839-5324.

Curriculum

Educational Videos
"Health Education for Non-readers," recommended for personnel working with patients, and "Diagnosis: The Emotional Impact," recommended for attending physicians and nurses, medical and nursing students, genetic counselors, and social workers, uses cystic fibrosis as case example. To order or for further information: Universal Health Associates, P.O. Box 65465, Washington, D.C. 20035, 202-429-9506.

Newsletters
The Treacher Collins Foundation Newsletter, P.O. Box 5, Concord, NH 03302-005.

The Chromosome 18 Communique, The Chromosome 18 Registry & Research Society, 6302 Fox Head, San Antonio, TX 78247.

General
Yearbook: "Cornelia de Lange Syndrome Album, 1989-90," a picture album of members' children. For information: Cornelia de Lange Syndrome Foundation, Inc., 60 Dyer Avenue, Collinsville, CT 06022, 800-223-8355.

A Handbook of Prenatal Screening for Major Fetal Disorders. Volume 1, Fetal Disorders Associated with Elevated MSAFP Values. To order or for information: Education Division, Foundation for Blood Research, P.O. Box 190, Scarborough, ME 04070-0190.

Letter to the Editor: "Allergic Reactions to Rubber in Patients with Myelodysplasia." *New England Journal of Medicine*, October 11, 1990. The authors, Elli Meeropol, Ruth Kelleher, Sheila Bell, and Robin Leger, are members of the New England Myelodysplaia Association, a subcommittee of the NERGG Consumer Concerns Committee.

GENERAL ANNOUNCEMENTS

New England Regional Camp for Girls and Young Women with PKU
Professionals from the New England Maternal PKU programs are in the process of finalizing plans for a week long camp for girls and young women with PKU. The program will be cenrally located in New England in a country setting for a one week period in June, 1991. The goal is to provide a place where young women can develop a sense of peer support and personal understanding of their condition. Participants, age 12 and over, who are either currently following the low pheylalanine diet or who have discontinued dietary restriction, will be encouraged to come together to discuss living with PKU and planning for the future. Many activities are being arranged including low protein cooking classes, films, and educational and exercise programs. Events will not all be diet-related. The camp is being supported through a grant form the Deborah Munroe Noonan Memorial Fund through the Bank of Boston, and also through a SPRANS grant from the Department of Health and Human Services, Division of Maternal and Child Health. There will e a registration fee of $25 per person, and transportation will be available if needed. Professionals who wish to volunteer their time are welcome to participate for part of the session or for the entire week. Additional information can be obtained from Kirsten Schnell or Mark Korson, M.D., at 617-735-7346.

REGIONAL GENETICS NETWORKS

Regional Genetic Networks, like the New England Regional Genetics Group (NERGG), have been established across the country. These networks usually consist of genetic service providers, public health planners, consumer groups, and federal and state maternal and child health personnel. Although the purpose and organization of each regional network may vary, all of the networks are committed to providing high quality genetic services and education in human genetics. The Council of Regional Networks (CORN) is made up of representatives of existing regional networks. The activities of CORN include communication between genetics networks, federal agencies and other groups involved with genetic services.

Region Name	States in Region	Region Name Abbreviation
Great Lakes Regional Genetics Group	IL, IN, MI, MN, OH, WI	GLaRGG
Great Plains Genetic Services Network	AR, IA, KS, ND, ND, NE, MO, OK, SD	GPGSN
Middle Atlantic Regional Human Genetics Network	DC, DE, MD, PA, VA, WV, NJ	MARHGN
Mountain States Regional Genetic Service Network	AZ, CO, MT, NM UT, WY	MSRGN
New England Regional Genetics Group	CT, MA, ME, NH RI, VT	NERGG
Genetic Network of the Empire State	NY	GENES
Pacific Northwest Regional Genetics Group	AK, ID, OR, WA	PacNORGG
Pacific Southwest Regional Genetics Group	CA, HI, NV	PacSW
Southeastern U.S. Regional Genetics Group	AL, FL, GA, KY, LA, MS, NC, SC, TN	SERGG
Texas	TX	TEXAS
Council of Regional Networks for Genetic Services	All Regional Networks	CORN

REGIONAL GENETIC NETWORKS

Southwest Regional Genetics Network
California State Department of Health Services
Maternal and Child Health Branch
Genetic Disease Section
2151 Berkely, Annex 4
Berkeley, CA 94704
415-540-2534
Contact: George C. Cunningham, M.D.

Mountain States Regional Genetics Services Newtork
Colorado Department of Health
Family Health Service Division
4210 East 11th Avenue
Denver, CO 80220
Contact: Robert S. McCurdy, M.D.

Southeastern Regional Genetics Group (SERGG)
Enory University School of Medicine
Office of the Treasurer
Atlanta, GA 30322
404-727-5840
Contact: Louis J. Elsas, II, M.D.

Midwest Regional Genetic Services Network (MRGSN)
Indiana State Board of Health
1330 West Michigan Street
Box 1964 Indiannapolis, IN 46206-1964
317-633-0805
Contact: F. John Meaney, Ph.D.

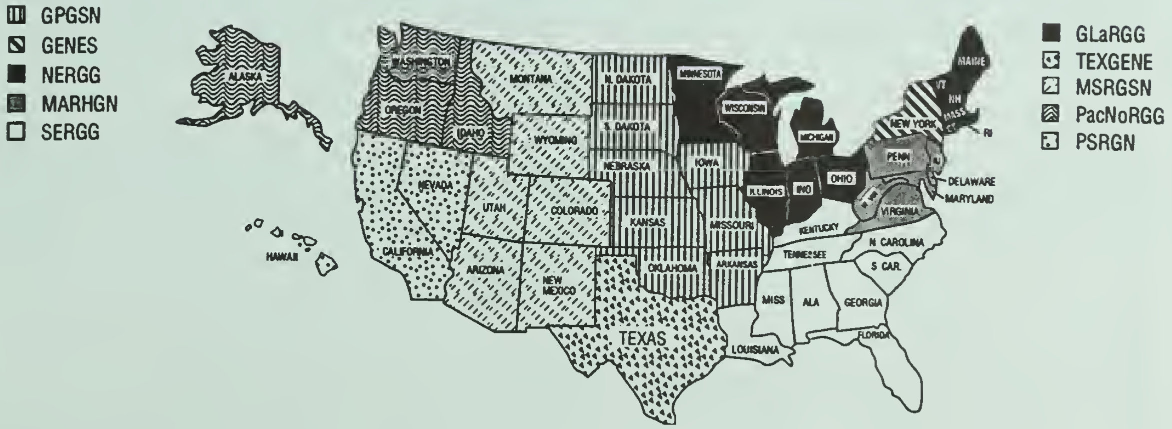
Great Plains Genetic Services Network (GPGSN)
The University of Iowa
Department of Pediatrics
Iowa City, IA 52242
319-356-2674
Contact: James A. Bartley, M.D.,Ph.D.

New England Regional Genetics Group (NERGG)
36 Ledge lane
P.O. Box 682
Gorham, ME 14038-0682
207-839-8637
Contact: A. Merrill Henderson

New York State Genetics Program
New York State Department of Health
Wadsworth Center for Laboratories and Research
Laboratory of Human Genetics
Albany, NY 12201
518-474-6796
Contact: Ann M. Willey, M.D.

Pacific Northwest Regional Genetics Network (PacNORGG)
The Oregon Health Sciences Unviersity
Crippled Children's Division
3181 Southwest Sam Jackson Park Roacd
Portland, OR 97201
503-225-8342
Contact: Victor D. Menashe, M.D.

Mid Atlantic Regional Human Genetics Network (MARHGN)
St. Chrisotpher's Hospital for Children
Genetics Department
Fifth and Lehigh Avenue
Philadelphia, PA 19133
215-427-5289
Contact: Hope H. Punnett, Ph.D.



Dedicated to

Marie M. Cullinane, R.N., M.S.

who died on March 8, 1991 after a long illness.

Marie was a member of the original staff that established the Developmental Evaluation Center (DEC) program, the Children's Hospital UAP, and developed the role of the nursing discipline as a valued member of the interdisciplinary team.- She devoted 23 years of professional service there, in which she exhibited a deep dedication to helping children and families. She held several different jobs during her tenure in the DEC all with great competence; she was most recently the Director of Client Services. Marie provided consultative assistance to several community agencies and parent groups in planning conferences and services as well as developing policies. She co-chaired (with Betsy Anderson) the Consumer Concerns Committee of NERGG from its inception.

Marie was an educator at heart; she taught those of us who worked with her in consistent messages. She was an instructor at Children's Hospital School of Nursing, and Adjunct Assistant Professor of Maternal Child Nursing at Boston College Graduate School of Nursing. As a former student said it, "Marie is the reason why I am in nursing today". She had lectured both nationally and internationally focusing on the health care and services for families having a child with disability. She shared her devotion to this same mission through numerous publications.

Marie was a caring person who fairly addressed those seeking her help; she was appreciated by everyone who knew her. She took a positive approach to life's daily encounters and enriched herself with a variety of personal interests. She loved animals; her dog Greta and cats Velvet and Reggie were very close. Music was a special love for Marie including strumming the dulcimer and her choral group. She enjoyed reading to the blind as well as giving time to assisting those unable to read attain these skills. Sketching was another hobby and Marie often honored us with one of her special creations.

Marie has helped many, taught many, and been loved by us all. We are grateful for her many years of comradeship and contribution. She will be greatly missed.

TERATOGEN INFORMATION

This column is designed to update readers on developments in the area of embryology and teratology and to describe the various teratogen-related monitoring, research and service activities in New England.

Neural Tube Disorders and Vitamins: An Overview

- *Elizabeth F. Allen, Ph.D. & Alan E. Guttmacher, M.D.*

The term neural tube disorder (NTD) refers to a malformation of the developing brain and spinal cord. A number of terms are used to describe NTDs, depending on the site and nature of the lesions. *Anencephaly* describes an NTD which results from a failure in closure of the tube at its cranial end, and thus includes absence of the cranial vault, cerebral hemispheres and sometimes the forebrain.[1] If the brain and spinal cord are open the disorder is *craniorachischisis*. These two malformations result in fetal or early neonatal death.[2] *Spina bifida* is a more general term referring to absence of vertebral arches. Such a defect which does not involve the skin or spinal cord (*spina bifida occulta*) rarely results in any handicap. However, in 80 to 90% of cases the lesion is open with protrusion of the meninges (*meningocele*) or the meninges and spinal cord (*meningomyelocele*). Meningomyelocele often results in loss of function below the level of the lesion and may be associated with hydrocephalus. An *encephalocele* is a lesion, usually in the occipital region, in which neurologic tissue protrudes through the skull.[2] These defects are believed to arise during the period 14 to 28 days after conception, or from the time of the first missed period to about the end of the 6th week post LMP.[3]

"Open" NTDs are those, such as anencephaly and most spina bifidas, in which the integrity of the fetal skin is disrupted. These can be detected prenatally because alpha-fetoprotein (AFP), a protein produced by the fetal liver, leaks into the amniotic fluid from the exposed fetal circulation. Since AFP passes into the mother's circulation from the amniotic fluid, its level can also be measured in samples of maternal serum (MSAFP), optimally at 15 to 18 weeks of pregnancy. Because of overlap in values between affected and unaffected fetuses, the cutoff which is used to detect most affected fetuses results in a high proportion of false-positive results. To distinguish affected fetuses from normal fetuses whose mothers have a high MSAFP result, further testing is necessary.[4] In the amniotic fluid, an elevated AFP value, in the presence of acetylcholinesterase (an enzyme present in the fetal nervous system) is diagnostic for open NTDs.[4]

The etiology of NTDs is not known. Both genetic and environmental factors are involved. Several epidemiologic observations are of interest. Geographic and racial/ethnic differences occur in NTD frequency, which is highest in the British Isles, parts of Pakistan and India, and Egypt and Lebanon. Irish and Sikhs have the highest frequencies; blacks, most Orientals and Ashkenazi Jews have the lowest. Members of populations with high risk actually lower their risk upon migration to a part of the world with a lower risk. The highest population frequency is 8-9/1000 births; the lowest is 0.1/1000. Worldwide the average is 1/1000; in the eastern U.S. it is 1-2/1000.[2,4] Seasonal and cyclic changes in frequency also occur.

Of interest is that the risks are higher for offspring of young teenagers or of women over 35, first-born or later than third-born, pregnancies immediately following a miscarriage, offspring of women with diabetes, pregnancies in lower socioeconomic classes, and relatives of affected individuals.[4] Several teratogens have been reported to increase the risk for NTDs, but the evidence is convincing only for valproic acid. However, MSAFP screening is recommended for women with concerns about exposure to alcohol, cocaine, solvents, or high fever in early pregnancy.

About 10% of NTDs are due to a chromosomal abnormality or a single gene syndrome. Familial recurrence risk in such cases depends upon the specific syndrome and its pattern of inheritance. For other cases, recurrence risks are based on a multifactorial inheritance model, which postulates the interaction of several genetic and environmental factors.[4]

A number of environmental factors, including nitrite-cured meat, blighted potatoes and hard water, have been proposed to cause NTDs, but on closer study have not appeared to do so.[2] A current suspect is diet deficient in vitamins, particularly folic acid. Supportive evidence for the role of diet comes from animal studies, from the higher frequency of vitamin deficient diet and of NTDs in lower socioeconomic groups, and the fact that the folic acid antagonist, aminopterin, appears to cause NTDs.

Studies done by Smithells *et al* reveal a highly significant difference in recurrence of NTDs when women who had already had at least one affected child were supplemented with vitamins for 4 weeks before conception and through the second missed menstrual period. Recurrence rate was 1/150 in the supplemented group, in contrast to 18/320 in the unsupplemented.[5,6] Another study of vitamin use reported greater reduction in recurrence rates in Northern Ireland than in south-east England and speculated that vitamin supplementation may be more important in areas with higher prevalence rates.[7] It may be that a genetic factor involved with folate metabolism is part of the multifactorial causation of NTD in some populations but not in others.[8]

A case-control study from Australia contacted mothers of 77 children with isolated NTDs within two years of the children's conception.[9] Controls were 77 mothers of children with a variety of birth defects, excluding NTDs, and 154 mothers of normal babies. The mothers were asked to complete a questionnaire regarding frequency of intake of 105 foods from three months before to nine months after conception. They were also asked about vitamin supplementation. 15% of both cases and normal controls had taken folate supplementation. When grouped by estimated amount of free folate taken, a protective effect appeared for those in the highest intake group - whose intake was 181 to 1678 micrograms/day. (RDA for pregnancy is 450 micrograms per day[10]) Association with total folate intake was much weaker. The authors speculate that mothers of affected babies may not handle dietary folate efficiently.

The first American epidemiological study of vitamins and the occurrence of NTDs was that of Mulinare *et al* .[11] It is also a case-control study, comparing vitamin intake in 347 mothers of children with NTDs to 2829 controls (both normal and affected). Women were interviewed at various times after delivery, sometimes as long as 15 years after. Users (about 14% of the group) were those who took vitamins at least 3 times a week from 3 months before until 3 months after conception. Nonusers (40% of the group) took vitamins less than 3 times a week. For whites vitamins appeared to have a protective effect, with a relative risk of 0.4 (95% CI 0.25 to 0.63) for vitamin users compared to nonusers. In the study's small number of blacks no effect was seen.

Mills et al, studied the pregnancy use of vitamins in over 1600 women of whom 517 had a child with a NTD, 546 a stillbirth or other malformation, and 573 a normal baby.[12] Women were questioned within one month of birth about multivitamin supplementation and fortified cereal consumption. The women were divided into three groups, by amount of supplementation for the period 30 days before to 45 after LMP; those who took [1] at least the RDA 6 days a week, [2] less than the RDA, and [3] none. No outcome difference was seen among these groups (15% of both normal controls and the NTD group were in group 1). The authors concluded "that the periconceptional use of multivitamins or folate-containing supplements by American women does not decrease the risk of having an infant with a neural-tube defect."

The third major U.S. study is by Milunsky *et al*, who prospectively interviewed women about vitamin intake at MSAFP screening or amniocentesis. The 22,776 pregnancies studied led to 49 cases of NTD (2.2/1000).[13] Women who took vitamins at least once a week from 3 months before until 3 months after conception were considered vitamin users (32% of the group). Nonusers took no vitamins during this period or took them only preconceptionally (14% of the group). NTD prevalence for nonusers was 11/3157 (3.5/1000); for users, 9/7261 (1.2/1000), which is a statistically significant difference. The authors then analyzed folate intake, but for this analysis looked at use starting in the first 6 weeks of pregnancy (probably the first six weeks post LMP, but it is unclear). Again those that took folate supplements early had a significantly lower frequency of NTDs.

It is difficult to compare all these studies. For example, the criteria used to separate users from nonusers differ. In the first three studies about 15% of women were classified as fully supplemented; in the last, taking one vitamin a week was considered adequate to classify a woman as a user, and the percent of users reached 32%. If a sizeable fraction of these were misclassified, the difference in frequency of NTD cases gets considerably smaller. Those interested in this controversy can read letters on the subject in the *New England Journal of Medicine.* [14]

Summary

The answer to whether vitamin supplementation can lower the *recurrence* of NTDs in populations with a high frequency appears to be "Yes." However, in spite of the generally impressive studies done to date by Smithells, yet another large prospective study is now being conducted in the British Isles because this question is still not settled in the minds of many.

The answer to the question of whether vitamin supplementation can lower the *occurrence* of NTDs in populations with relatively low incidence is still unknown. Perhaps a prospective study, with measurement of vitamin levels in blood samples during early pregnancy, would be able to reconcile the differing results of the four epidemiological studies mentioned above.

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Elizabeth Allen is the Coordinator of the Pregnancy Risk Informaton Service at the Vermont Regional Genetics Center. Alan Guttmacher is the Director of the Vermont Regional Genetics Center. This article was adapted from the Vermont Pregnancy Risk Information Service Newlsetter, began in 1989 as a combined effort of the University of Vermont College of Medicine, the Vermont Department of Health, and the Vermont Chapter of the March of Dimes Birth Defects Foundation. Views expressed in this newsletter are those of the authors and are provided as general background information only, based on information available as of April, 1990. Clinical practice must be determined by individual health care providers, who should seek up-to-date information.

Neural Tube Disorders and Vitamins: A Commentary on the Current State of Research

- Lewis B. Holmes, M.D.

When it was first suggested that neural tube disorders (NTDs) might be prevented by periconceptional supplementation with vitamins, there was hope this would be confirmed promptly by well-designed studies. Thus far, the results of three large-scale studies (1-3) have been published, but no clear answers have emerged. At a meeting called by the Spina Bifida Association of America in December, 1989, the consensus among most, but not all, clinicians and epidemiologists with experience on this subject was that the two positive studies (1,3) could be showing the protective effect of the "vitamin taker" rather than the vitamins or the folate. Significant deficiencies in study design were noted in each of these three studies. There is hope that an ongoing prospective study in Budapest, Hungary, of the preventive effects of vitamin supplement will clarify the issue. This is a randomized study of the occurence, not recurrence, of NTDs and other malformations. In a few years the data will be available from the randomized trial in the U.K. (and other countries) which will assess whether periconceptional vitamin supplementation will prevent the recurrence, not occurence, of a neural tube disorder after the birth of the first affected child. A large scale study is being proposed now in Northern China, a region in which the prevalence rate of neural tube disorders is much higher than in the U.S. or U.K. in association with well-documented dietary deficincies. A study of the effects of periconceptional vitamins on the occurrence, not recurrence, of NTDs is proposed with U.S. financial support. However, there is concern the sitruation in China may be so different that the findings will have limited value for North American physicians. So, for now, the possibility of understanding the relationship between neural tube disorders and vitamins has not been settled. We can hope it will be...soon.

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New England Teratogen Information Services

The following Teratogen Information Services provide information to the public and health professionals regarding potential risks from environmental exposures .

MA

Pregnancy Environmental Hotline
National Birth Defects Center
Fransiscan Children's Hospital
30 Warren Street
Brighton, MA 02135
617-787-4957
800-322-5014 (in Massachussetts only)

CT

Pregnancy Exposure-Risk Line
University of Connecticut Health Center
Farmington, CT 06032
203-679-1500
800-325-5391

VT

Pregnancy Risk Information Service
Vermont Regional Genetics Center
96 Colchester Avenue
Burlington, VT 05401
802-658-4310
800-531-9800

GENETIC COUNSELING BRIEFS

Over the past two decades knowledge in genetics has expanded and the commercialization of research has made available numerous technologies for the screening, diagnosis and treatment of human genetic diseases. Due to this growth the need for highly trained professionals in genetics has increased. There is a growing demand for health care professionals with training in genetics to work in clinics, hospitals, physician practices, teaching institutions, laboratories, research, public health programs, and in the private sector. Developments in the field of genetic counseling and two professional organizations are profiled in this issue of ***The Genetic Resource****.*

Genetic Counseling

Genetic counselors, sometimes referred to as genetic associates, are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling. Most enter the field from a variety of disciplines, including, biology, genetics, nursing, psychology, public health and social work. Genetic counselors work as members of a health care team, providing information and support to individuals and families who have a personal or family history of birth defects, who may be at risk for a variety of inherited conditions, or who are interested in receiving information about currently available genetic disease screening and diagnostic tests. Genetic counselors are trained to identify families at risk, investigate the disability present in the family, interpret information about the condition, analyze inheritance patterns and risks of recurrence and review available testing and treatment options. Genetic counselors also provide supportive counseling to families, serve as patient advocates and refer individuals and families to community or state support services. Many genetic counselors serve as educators and resource personnel for other health professionals and for the general public. Some also work in varying administrative capacities. Many engage in research activities related to the field of medical genetics and genetic counseling. Certification for eligible candidates is available through the American Board of Medical Genetics (ABMG). Requirements for certification include training at sites accredited by the ABMG, documentation of genetic counseling experience, evidence of continuing education and successful completion of a comprehensive ABMG certification examination. There are approximately twelve training programs in the United States and one in Canada that offer a Master's degree in genetic counseling. Most require two years of study. Coursework typically includes clinical or medical genetics, cytogenetics and molecular genetics coupled with psychosocial theory and counseling techniques. Clinical placement in medical genetic centers is an integral part of most training programs.

National Society of Genetic Counselors (NSGC)

Growth within the genetic counseling profession spawned the development of the The National Society of Genetic Counselors (NSGC). Incorporated in 1979, the NSGC has as its primary goal to promote the professional interests of genetic counselors and to provide a network for professional communications. While the NSGC strives to meet the needs and interests of genetic counselors, any professional whose interest focuses on genetic counseling is eligible for membership. The NSGC is governed by a Board of Directors and has a number of active committees, including an Education Committee, Social Issues Committee, Professional Issues Committee, Finance Committee, Membership Committee, and Nominating Committee. A number of Ad Hoc Committees also exist. NSGC members serve as liaison persons or on working committees of numerous organizations. In addition, the NSGC publishes a quarterly newsletter, *Perspectives in Genetic Counseling*, for its members and will publish, beginning in 1992, the *Journal of Genetic Counseling*. Regional educational meetings and an annual conference have also been established by the NSGC. The NSGC held its 10th Annual Education Conference, *The Interface Between Public Health and Clinical Genetics*, in Cincinnati (October 14-16 1990). Other activities organized by the NSGC include, 1) a jobs hotline service connecting members and graduate students with job opportunities that meet their career goals, 2) a membership directory available for professional and personal use, 3) a legislative update service, and 4) a bi-annual professional issues survey addressing issues of compensation, job responsibilities and directions, benefits and the changing nature of the profession. ***For more information about the activities of the National Society of Genetic Counselors, or to inquire about membership, contact:*** *Bea Leopold, Executive Director, 233 Canterbury Drive Wallingford, PA, 19086 (215) 872-7608.*

Single Gene Counselors

Single gene counselors, also referred to as "single disorder counselors," are a new group of professionals emerging in response to the growing need for trained genetic specialists in health care and the shortage of master's level trained genetic counselors. The premise is that the transmission of information to individuals with single gene disorders can be achieved by persons who receive special training but do not have a traditional genetic counseling background. For example, there are now hemoglobin trait counselors for sickle cell disease and thalassemia. Accredited training programs that offer counselor certification have been established by public health programs or individual centers to educate sickle cell counselors to provide information and referral services related to newborn, prenatal and general population screening. While there currently are not any national standards for training, this type of certifying process is likely to evolve and to be used in the future for other disorders. With the potential for mass population screening for heterozygote detection of cystic fibrosis it is anticipated that there will be cystic fibrosis counselors and other genetic disease-specific counseling specialists in the near future. In addition to single disorder counselors, other specialists such as genetic educators, genetic intepreters, and genetic aides, sometimes also referred to as "non-master level" (NML) counselors, are providing a growing number of genetic services. Many of the NML counselors have a master's degree in areas other than genetic counseling. A number of centers currently utilize NML counselors to coordinate maternal serum alpha-fetoprotein (MSAFP) screening programs. These counselors provide education to health professionals, and administer the handling and reporting of test results. Bilingual or multilingual genetic interpreters are also increasingly being used to assist in patient counseling sessions. A wide variety of professional and consumer educational services are developed and implemented by genetic educators. It is expected that additional programs to train single disorder counselors and other genetic specialists will be needed to meet the escalating demand for genetic counseling services. This approach is expected to improve the quality of genetic services in all population groups, including the underserved, culturally diverse populations, to create new employment opportunities, and to expand the current role of the genetic counselor. While the logistics of training and supervision need to be addressed in greater depth, it is expected that single gene counselors and other genetic specialists will become a valuable part of the health care team in the next decade.

International Society of Nurses in Genetics (ISONG)

Nurses are in a unique position to provide genetic health care services. There are many roles and settings in which nurses can collect important medical and family information in order to assess a patient's risk for the occurrence of a genetic disease. Nurses in public health, obstetrics, pediatrics, medical, surgical, psychiatric, geriatric, and ambulatory care are in a unique position to identify families at risk, provide genetics education, refer those in need of genetic services, interpret genetic information, help families cope when affected by a genetic disorder, and serve as an advocate for families to assure access to services. In 1988 the International Society of Nurses in Genetics (ISONG) was formed as a result of growing interest among nurses already working in genetics to establish a formal professional organization. The purpose of the International Society of Nurses in Genetics is to foster scientific and professional growth of nurses in human genetics. The goals are to 1) provide a forum to promote the integration of the nursing process in the delivery of genetic health care services, 2) encourage incorporation of principles of human genetics at all levels of nursing education, 3) promote development of standards of practice for nurses in human genetics, 4) advance nursing research in human genetics and 5) provide a forum for dialogue with other members of the nursing and genetics communities. ISONG currently has a membership of over 100 nurses and its members continue to be extremely active. The organization anticipates that membership will increase over the next few years as more nurses receive training in human genetics. ISONG holds its annual professional meeting just prior to the annual meeting of the National Society of Genetic Counselors (NSGC) and the American Society of Human Genetics (ASHG). In addition, ISONG publishes a newsletter for nurses interested in genetics. ***For information regarding ISONG membership contact:*** *Shirley Jones, R.N., M.S., Genetics and IVF Institute, 3020 Javier Road, Fairfax, Virginia 22031 (703) 698-7355. For information about the newlsetter contact: Lynette Wright, R.N., M.P.H., c/o Georgia Genetics, Inc. 5775 Glenridge Drive, Building A, Suite 150, Atlanta, Georgia, 30328 (404) 634-4248.*

Training for Nurses in Genetics in New England

The Shriver Center/ University Affiliated Program offers a one year program to prepare clinical nurse specialists in genetics. Students must be currently enrolled in a Master of Science nursing program. The program consists of a two semester course consisting of didactic material and clinical experience at The Shriver Center for Mental Retardation under the direction of Dr. Marvin Natowicz and Catherine Bove. Opportunities for clinical experience are also available at other centers in the Boston area. A modest stipend is available to full-time nursing students who enroll in this program. ***For more information contact:*** *Mary Challela, R.N., D.N.SC., Shriver Center for Mental Retardation, 200 Trapelo Road, Waltham, Massachusetts, 02254 (617) 642-0268.*

Genetic Applications A Training Program in Genetics for Health Professionals

Genetics Applications for Health Professionals is a short term, interdisciplinary educational program in applied genetics designed for community or hospital-based health professionals. The goals of the program are to help professionals 1) become aware of the various roles of health professionals in the provision of genetic services, 2) explain and update basic genetic information and to identify how genetic information can be incorporated into individual practice, 3) recognize individuals who may be at risk because of family history, physical findings or exposure to environmental hazards, 4) become knowledgeable of indications and procedures for referral to genetic counseling services, and 5) assist concerned individuals in locating and using appropriate local, regional, and national resources. Genetic Applications has been developed and packaged for delivery in a number of formats including, three all-day sessions for lectures and discussions, self-instructional units including reading and special assignments, and computer assisted tutorials for home use. The development of this course was funded by the Office of Maternal and Child Health, U.S. Department of Health and Human Services. The project is a collaborative effort at the University of Colorado Health Sciences Center between the School of Nursing and School of Medicine, Genetics Unit, working in cooperation with the Mountain States Regional Genetic Services Network. ***For more information contact:*** *Eunice Shishmanian, R.N., Developmental Evaluation Center, The Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, 617-735-6501.*

LEGAL NOTES

This column is designed to update readers on significant current medicolegal and social policy issues and the extent and manner in which these issues impact upon the practitioner, consumer, consumer's family, society, legislature and courts.

Carrier Screening for Cystic Fibrosis: A Commentary on Current Legal and Social Policy Issues

- *Philip R. Reilly, M.D., J.D.*

The identification and cloning of the gene mutations which cause cystic fibrosis is surely one of the most dramatic developments in human molecular biology. Our knowledge of the protein that the gene encodes is increasing rapidly, and hopes for developing new therapies for this common lethal disorder are running high. Localization of the gene has spurred a tremendous effort to identify all its mutations, and it has created the possibility of testing individuals to determine if they are carriers.

Given that about 1 in 25 whites of Northern European extraction is a carrier *(millions of Americans)*, commercial and clinical interest is high. Already at least six companies offer carrier testing for about $150-$200.

The advent of CF carrier testing has provoked sometimes heated debate over the circumstances under which it is appropriate to offer it to persons *without* a family history for the disorder. This debate is heavily influenced by earlier testing efforts designed to detect carriers of sickle cell anemia and Tay Sachs disease, efforts that contrast sharply. In the early seventies sickle cell programs were marred by shoddy legislation, poor planning and inattention to the privacy interests and counseling needs of patients. At the same timeTay-Sachs testing, premised on community education and access to genetic counseling, prospered. Fortunately, sickle cell testing efforts today are well organized, but there is a strong concern that we should not repeat earlier errors.

Unfortunately, testing for CF is not straightforward. Currently, testing for the major mutation and uncommon ones permits detection of about 85% of carriers in some ethnic groups. But a negative test does *not* rule out being a carrier; it reduces one's risk to about 1 in 150. This is a special problem for couples one of whom has tested negatively and one of whom is a carrier. They still face about a 1 in 600 risk of bearing a child with CF. The limitations of the test and a concern that the nation lacks the resources to provide adequate genetic counseling to persons being tested led the American Society of Human Genetics in October 1989 to take the unprecedented step of issuing a statement that routine CF carrier testing of pregnant women and other individuals "was **NOT** yet the standard of care in medical practice." It also called for pilot programs to study how best to develop CF testing programs. In March 1990 the NIH convened a workshop on CF screening. Influenced partly by the fact that the power to detect carriers was increasing steadily (the original test for the major mutation identified only 70 percent of carriers), the workshop urged that pilot testing programs be funded. It also acknowledged that the argument for testing grew as we approached a 90 to 95 percent detection level. That document, the most comprehensive to date on the subject, is reprinted below.

When the detection rate reaches the 90 percent level, I think the argument in favor of requiring physicians to inform persons about the test regardless of a family history outweighs that against. At this point only two of the NIH workshop participants' four reasons against wide-scale testing would remain: 1) that the frequency of the gene varies substantially across ethnic and racial groups (which complicates the utility of the test and the counseling process), and 2) that there will be problems in educating physicians and counseling patients about test results.

The first problem is relatively straightforward to solve. It requires gene frequency data, which should emerge rapidly. A consortium of about 80 laboratories around the world has already collected much of these data. As the for the second, the debate will focus on whether physicians, especially obstetricians, and other health care providers are able to appropriately offer the test, which includes helping patients understand the results. In essence, this is a debate about the future of genetic counseling — a relatively new profession — and the manner in which genetic testing is offered in our society.

As the array of carrier tests grows and the cost of testing drops, genetic counseling is likely to earn a place in primary care. The argument that primary care providers will not be able to provide adequate genetic counseling must be measured against the patient's right to know about a potentially helpful test. At some point (which may ultimately be decided by the courts) this right to know invokes a corresponding obligation upon the physician to inform about the test (and counsel or refer for counseling). At this juncture the duty to inform becomes an obligation.

The debate about when, to whom and how to offer CF carrier testing merits full discussion. CF testing is a paradigm for many other genetic tests that will someday be routinely offered as part of preventive medicine. This is why pilot testing and counseling projects are so needed. The consensus that emerges from the study of CF testing will be a benchmark for other efforts.

Philip R. Reilly is a clinical geneticist and an attorney. He is Executive Director for the Shriver Center for Mental Retardation, Inc. Dr. Reilly is Chairman of the Social Issues Committee of the American Society of Human Genetics. He currently serves on advisory boards for the Office of Technology Assessment (OTA), National Academy of Sciences (NAS) and Institute of Medicine (IOM) in Washington on projects pertaining to human genetics. He is also a consultant to two genetic testing companies.

Statement from the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene

Cystic Fibrosis is an autosomal recessive genetic disorder clinically characterized by chronic lung disease and pancreatic insufficiency. Median survival is 25 years, with an increasing number of patients surviving into their 30s. This disease affects about 1 in 2500 persons of European ancestry. It is less frequent among black and Hispanic Americans and is rare in Asians. One in 25 persons of European ancestry is a carrier, having one normal and one abnormal cystic fibrosis gene.

The cloning of the cystic fibrosis gene and identification of the most common mutation in the gene were major advances in medical genetics. These breakthroughs provide a basis for understanding the pathophysiology of the disease and offer the hope that improved therapy can be developed. In addition, there are immediate implications for the identification of carriers of a mutant cystic fibrosis gene.

Currently DNA analysis can identify a single mutation in the cystic fibrosis gene that is present in 70 to 75 percent of carriers of European ancestry. Many additional mutations producing cystic fibrosis, currently about 20, have been identified. The identification of multiple individually rare mutations rather than a small number of common mutations will make carrier testing more difficult. The inability to detect all carriers creates complexities for the use of carrier testing at this time. A major question is whether population-based screening for cystic fibrosis carriers could or should be implemented at present. Population-based screening implies offering a program of carrier testing, with appropriate informed consent and genetic counseling, to potentially millions of healthy people. The purpose of such screening would be to allow people to make more informed reproductive decisions with regard to the risk of cystic fibrosis in their offspring.

Unlike testing in the general population, testing for carriers in families in which the disease has occured is nearly 100 percent informative. This is because carrier testing can be performed with linkage analysis in addition to mutation analysis when there is a DNA sample available from an affected person in the family. Therefore, testing should be offered to all individuals and couples with a family history of cystic fibrosis. This makes it more important than ever for providers of medical care to obtain family histories, particularly for patients of reproductive age.

In contrast, for a number of reasons there is a consensus that under the current circumstances population-based screening should not be recommended for individuals and couples with a negative family history. First among these reasons is the fact that currently the test will detect only 70 to 75 percent of carriers. Therefore, only about half of the couples at risk can be identified. Second, the frequency of the disease and the different mutations vary according to racial and ethnic background, so that important laboratory and counseling modifications would be required in different populations. Third, there are substantial limitations on the ability to educate people regarding the use of an imperfect test. Fourth, without more definitive tests, about 1 in 15 couples-those in which one partner has a positive test and the other has a negative test-would be left at increased risk (approximately 1 in 500) of bearing a child with cystic fibrosis.

These difficulties would be substantially reduced if testing could detect at least 90 to 95 percent of carriers. There is a consensus that population-based screening for carriers could be offered to all persons of reproductive age if a 95 percent level of carrier detection were achieved. The offering of population-based screening would still require that substantial educational and counseling guidelines be satisfied. Benefits and risks of population-based screening and its feasibility are uncertain if this level of carrier detection cannot be achieved.

Regardless of when or whether population-based screening becomes widespread, there is consensus on a number of screening guidelines. First, screening should be voluntary, and confidentiality must be assured. Second, screening requires informed consent. Pretest education material should explain the hazards (for example, psychological effects and the loss of insurability) and benefits of choosing to be tested or not choosing to be tested. Third, providers of screening services have the obligation to ensure that adequate education and counseling are included in the program. Fourth, quality control of all aspects of the laboratory testing, including systematic proficiency testing, is required and should be implemented as soon as possible. And finally, there should be equal access to testing.

In view of the importance of the voluntary nature of screening and anticipated rapid changes in current informaton, legislative action to require cystic fibrosis screening is undesirable at present. There is consensus, however, that cystic fibrosis carriers should not be discriminated against with regard to insurability or employment. If evidence of discrimination emerges, corrective legislative action should be considered.

When population-based screening becomes available, who should be offered testing and in what setting? The most appropriate group for population-based screening comprises those of reproductive age. Although it is recognized that testing will often be provided to couples during pregnancy, it is preferable to offer screening before conception. Preconception testing offers a couple that has a one-in-four risk of having an affected child a broader range of reproductive options.

The optimal setting for carrier testing is through primary health care providers. Community-based screening programs provide an alternative setting. At present, newborn screening primarily to detect carriers is inappropriate, as are screening programs directed at children below reproductive age.

Education of the lay community and health care providers concerning the disease, its genetic transmission, and carrier testing is an important goal. Both traditional and innovative methods should be used for community education. Education regarding carrier testing for cystic fibrosis could have a major effect on the level of genetic knowledge in the population.

In addition to obtaining informed consent, providers of carrier screening must ensure the availability of appropriate genetic counseling. Those with a negative carrier test should require minimal counseling but should be reminded of the limitations of the test. Those identified as carriers should be informed of the personal and family implications of their status. Group and individual counseling services should be available. After specialized training, physicians, nurses, social workers, and other health care personnel could provide much of this counseling service. A range of teaching devices to be shared with family members should be developed and evaluated as an adjunct to counseling.

Couples found to have a one-in-four risk require comprehensive individual genetic counseling by a qualified professional. This counseling should be non-directive and should help the couple to make reproductive decisions consonant with their own beliefs. Educational materials that present a range of views and options should be developed.

Pilot programs investigating research questions in the delivery of population-based screening for cystic fibrosis carriers are urgently needed. These programs should address clearly defined questions, including the effectiveness of educational materials, the level of utilization of screening, laboratory aspects, counseling issues, costs, and the beneficial and deleterious effects of screening. One important issue is to determine the effect on couples who are at increased risk because only one partner has an identified cystic fibrosis mutation. Pilot programs should examine alternative models of delivery that could be generalized. Federal funds are critically needed to carry out these programs.

The development of carrier-screening programs for cystic fibrosis should not detract from the current scientific efforts to improve the treatment of this disease. Currently, about 30,000 Americans have cystic fibrosis, and additional children with the disease are born every day. The ability to identify couples at risk will continue to be important even if more successful treatments are developed.

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New England Regional Genetics Group (NERGG) Policy Statement on Screening for Cystic Fibrosis

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Statement on Screening for Cystic Fibrosis

The discovery of the CF gene and the identification of the major causative mutation (ΔF508) raises great hope for the development of new treatments of the disease, and for the first time makes possible the identification of gene carriers. It is the consensus of the New England Regional Genetics Group (NERGG) that:

1. Carrier testing should be offered to individuals with a family history of cystic fibrosis (CF), or to couples in which a partner has a family history of CF. In such cases, carrier testing is considered a medical necessity and no longer within the realm of medical research.

2. Programs of systematic population based screening are inappropriate at the present time. It is recognized, nevertheless, that some individuals with no family history of CF may be motivated to seek carrier testing. This is a personal decision that they are free to make.

3. Given the present state of the test, physicians and other health care practitioners should not currently be expected to inform individuals with no family history of CF about this test.

4. Laboratory testing should be offered ONLY in conjunction with support programs that will provide appropriate education and counseling to the public. In addition, approaches should be developed to plan the most effective ways to reach the target population.

5. Quality assurance programs must be developed for CF testing.

6. There is a recognized need for professional education. It is the joint responsibility of laboratories and practicing geneticists to develop programs to meet this need.

In general, these conclusions are in accord with the statement of November 13, 1989, by the American Society of Human Genetics.

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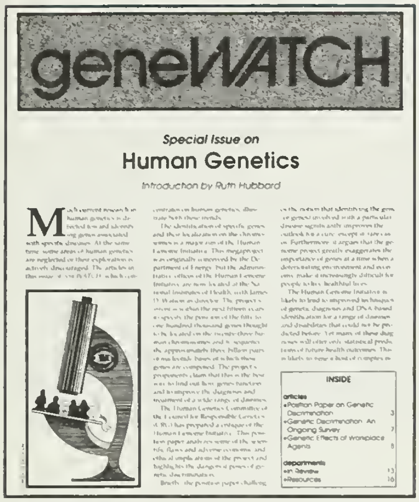
This NERGG Policy Statement is an evolving recommendation which will periodically be updated as new information becomes known.

CITIZEN INTERESTS

Citizen participation in issues relating to health care and genetic services is of great importance. An awareness and understanding of consumer concerns is essential for health professionals and policy makers. This column describes selected public interest groups and consumer advocacy organizations that are involved in discussions about genetic-related issues.

Council for Responsible Genetics (CRG)



geneWATCH

Special Issue on
Human Genetics
Introduction by Ruth Hubbard

INSIDE
articles
- Position Paper on Genetic Discrimination 3
- Genetic Discrimination: An Ongoing Survey 7
- Genetic Effects of Workplace Agents 8

departments
- In Review 13
- Resources 16

The Council for Responsible Genetics (CRG) is a Boston-based national non-profit organization that is committed to raising the social and ethical questions associated with biotechnology.

The Council monitors developments in biotechnology in the United States and abroad and alerts the general public to the serious questions they raise. The Council has active program initiatives in the following three crucial areas: 1) preventing the militarization of biological research, 2) countering genetic discrimination and 3) expanding public participation in decisions about the release of genetically engineered organisms into the environment. The Council for Responsible Genetics is currently initiating a new campaign to counter genetic discrimination and the creation of a class of people who are considered unemployable and uninsurable because of their genes. The campaign will focus on the Boston area and the state of Massachusetts as a model fo developing a comprehensive program intended to prevent this new form of discrimination. The CRG publishes *GeneWatch*, a quarterly newsletter devoted to analyzing the politics, ethics and social impact of new biotechnologies both in the U.S and abroad. *Genewatch* includes feature articles, news, and notes and reviews topics such as bioweapons research, genetic discrimination, novel organisms in the environment and war. Non-technical, with resources and contact for activists. Sample $2.00/6 issues for $24.00. ***For more information contact:*** *Nachama Wilker, Executive Director, Council for Responsible Genetics (CRG), 19 Garden Street, Cambridge, MA 02138, 617-868-0870.*

The Genetic Screening Study Group

The Genetic Screening Study Group is a Boston-based group composed of persons from various disciplines including medicine, philosophy, science, journalism, clinical genetics and epidemiology. The group meets every two weeks to discuss social policy and ethical issues in medical genetics as they relate to genetic testing. The group is currently pursuing two projects. The first is a study on discrimination based on genetic screening tests. Members of various genetic disease support groups are being surveyed for cases of discrimination in insurance, employment and other social arenas. The data will be used to inform social policy on these issues. Secondly, the group is planning its fourth annual conference called *"Genes and Human Behavior: A New Era?"* for scientists and journalists on October 26, 1991 (see announcement and registration information on page 111). The program will involve a critical look at the history of this field, media coverage of human behavioral genetics, presentations on genetics and mental illness and genetics and alcoholism, and the implications of new techniques for studying the genetics of human behavior. The genetic screening study group is interested in broadening its discussion groups and welcomes participation from people from all backgrounds. ***For more information contact:*** *Jon Beckwith, Ph.D., at 617-423-1920 or Marvin Natowicz, M.D., Ph.D., at 617-642-0176.*

The Project on Women and Disability

The Project on Women and Disability was established in 1987 in Boston, Massachusetts. The primary goal of The Project on Women and Disability is to give women a stronger voice in both the Disablity Rights Movement and the Women's Movement. This is done by 1) encouraging women with disabilties to speak out on issues of importance to them, 2) educating disability organizations and women's organizations on the life experience and needs of disabled women by providing education, training, and technical assistance (such as for accessiblity and attitudinal awareness), 3) reaching and involving under-represented disabled women including disabled women of color, disabled mothers, and teenage and older disabled women, and 4) identifying and training people in key positions to effect positive change. This includes family members of disabled people, health care workers, educators and human service workers, the media, legislators and others. The Project on Women and Disability has conducted disability awareness workshops for numerous groups, including members of the New England Regional Genetics Group (NERGG). ***For more information contact:*** *Marsha Saxton, Director, Project on Women and Disability, One Ashburton Place, Room 1305, Boston, MA 02108, 617-727-7440, (voice and TDD).*

Collaboration Among Parents and Professionals (CAPP): National Parent Resource Center

The CAPP National Parent Resource Center is a parent-run resource system designed to further the goals of family centered, community-based, coordinated care for children with special health care needs and their families. The CAPP/NPR central office at the Federation for Children with Special Needs in Boston, Massachusetts, provides national coordination. Four regional centers and eight National Resource Parents are located around the country, ensuring grassroots input, expertise, and a broad national perspective. The purpose of the CAPP/NPR Center is to develop a parent organized, national coordinated system that will maintain and strengthen parent and family invovlement in health care. This project is built upon the recognition that understanding the needs of families is central to achieving this nation's agenda for family-centered, community-based, coordinated care. The project is implemented in conjunction with the Technical Assistance for Parent Programs (TAPP) Project, which assists Parent Training and Information (PTI) projects nationwide to inform families about special education classes. The CAPP/NPR Center provides assistance for individual families on a wide range of topics for children with special health needs. In addition, written materials training packages, workshops, and presentations for parents and professionals on health care financing, special education, parent/professional collaboration and other topics are available.. ***For more information contact:*** *Betsy Anderson, Director, CAPP, Federation for Children with Special Needs, 95 Berkeley Street, Suite 104, Boston, MA 02116, 617-482-2915.*

Partners for Disabled Youth

Partners for Disabled Youth is a non-profit organization providing role-model relationships between disabled youths and adults. Partners arranges for one-to-one relationships between adolescents and children with disabilities and adults who have similar disabilities. Partners' goals are 1) to provide a role model through which the young Partner can explore creative fun and socialization, 2) to inspire the youth to develop his/her talents and abilities by means of an appropriate role model who has encountered the same frustrations, and has experienced success. An Adult Partner addresses the need for the child with a disability to develop a supportive relationship with a caring adult who has the same or similar disability, 4) to develop the awareness of opportunities and broadening of experiences, 5) to provide an opportunity for adult volunteers to contribute their unique backgrounds and experiences of a disabled child, and 6) to increase self-esteem and motivation in the lives of disabled youth. ***For more information contact:*** *Partners for Disabled Youth, Inc., c/o Office of Massachusetts Office on Disability, One Ashburton Place, Room 1305, Boston, MA 02108, 617-727-7440 (Voice and TDD), 800-322-2020.*

GENETICS & BIOTECHNOLOGY

This column describes activities related to biotechnology in the New England Region. It is designed to familiarize practitioners and consumers with the field of biotechnology as it relates to human health care and it includes general information on companies, reports and events that may be of interest.

Genetics, Biotechnology & Public Health

A one day regional symposium titled, *Genetics, Biotechnology and Public Health* was held at the Brigham and Women's Hospital in Boston, Massachusetts in December of 1990. This event was the third in a series of educational symposia designed to bring together representatives from academia, industry and government. Over 100 participants from these different groups attended to learn about the cutting edge developments in the area of human genetics. This event was co-sponsored by the Massachusetts Centers of Excellence Corporation, Brigham and Women's Hospital, Massachusetts Genetics Program of the Massachusetts Department of Public Health, the Massachusetts Biotechnology Reserach Institute, and the Massachusetts Biotechnology Council. ***For a copy of the Symposium Report contact:*** *Fernando Quezada, Executive Director, Biotechnology Center of Excellence, 9 Park Street, Boston, MA 02111 (617) 727-7430.*

New England Governors' Conference, Inc.

One of the most rapidly developing industries in New England is commercial biotechnology. This industry is expected to play a major role in the New England economy over the next decade. The abundance of medical schools, teaching hospitals, research institutes, venture capital sources and the collaboration among the private and public sector in New England is expected to greatly contribute to this emerging industry. The New England Governors' Conference, Inc., through its Technology Advisory Council, formed the New England Biotechnology Cooperative in 1988. Members of the Cooperative represent biotechnology firms, universities, and government. The Cooperative encourages the sharing of ideas, the development of programs, the identification of issues which may affect the industry's growth, and the marketing of the Region's biotechnology expertise to benefit New England. The New England Governors' Conference held its Second Annual Conference on Biotechnology titled, *"Biotechnology... The Growth Industry of the 1990's"* in Connecticut in October 1990 to examine the state of the industry and to determine how New England can maintain its momentum in the field. ***For more information contact:*** *New England Governors' Conference, Inc., 76 Summer Street, Boston, MA 02110-126 (617) 423-6900.*

New Reports on Biotechnology

A new 150 page guide, called the **Massachusetts Biotechnology Industry/Education Resource Directory: Guide to Schools, Careers, and Biotechnology Companies**, has been developed by Bay State Skills Corporation (BSSC). BSSC is a quasi-public corporation founded in 1981. BSSC funds educational institutions in cooperation with industry to prepare individuals to acquire the skills necessary to compete in a technological and global economy. This guide contains information about educational programs, job opportunities, biotechnology commpanies and parternships and collaborations that promote science education in Massachusetts. ***For more information contact:*** *Fenna Hanes, Bay State Skills Corporation, 101 Summer Street, Boston, MA, 02110 (617) 292-5100.*

Another report, titled **An Assesment of the Masssachusetts Biotechnology Industry,** was prepared by Peter Feinstein, Inc., and released in October of 1990. This report, a project of the Massachusetts Centers of Excellence Corporation, Bay State Skills Corporation and the Massachusetts Biotechnology Council, Inc,. describes the status of the biotechnology industry in Massachusetts. ***For more information contact:*** *Peter Feinstein, Inc., One Kendall Square, Cambridge, MA 02139 (617) 577-8110.*

Biotechnology Newlsetter

The BIOLINE, a quarterly publication of the Massachusetts Biotechnology Council, Inc. ***For more information contact:*** *MBC, One Kendall Square, Building 600-Suite 315, Cambridge, MA 02139, (617) 577-8198.*

Patents of Particular Interest

Integrated Genetics has acquired exclusive rights to develop a new technique that will allow fetal cell sampling from a pregnant women's blood rather than through amniocentesis for prenatal screening and diagnosis. This technology was developed by Dr. Diana Bianchi and colleagues at The Children's Hospital in Boston, Massachusetts.

EDUCATIONAL RESOURCES

This column features new genetics educational materials that may be of interest to health care providers and/or to consumers. For information about other existing educational materials, please contact your State Genetics Program.

Genetic Testing for Cystic Fibrosis A Handbook for Professionals

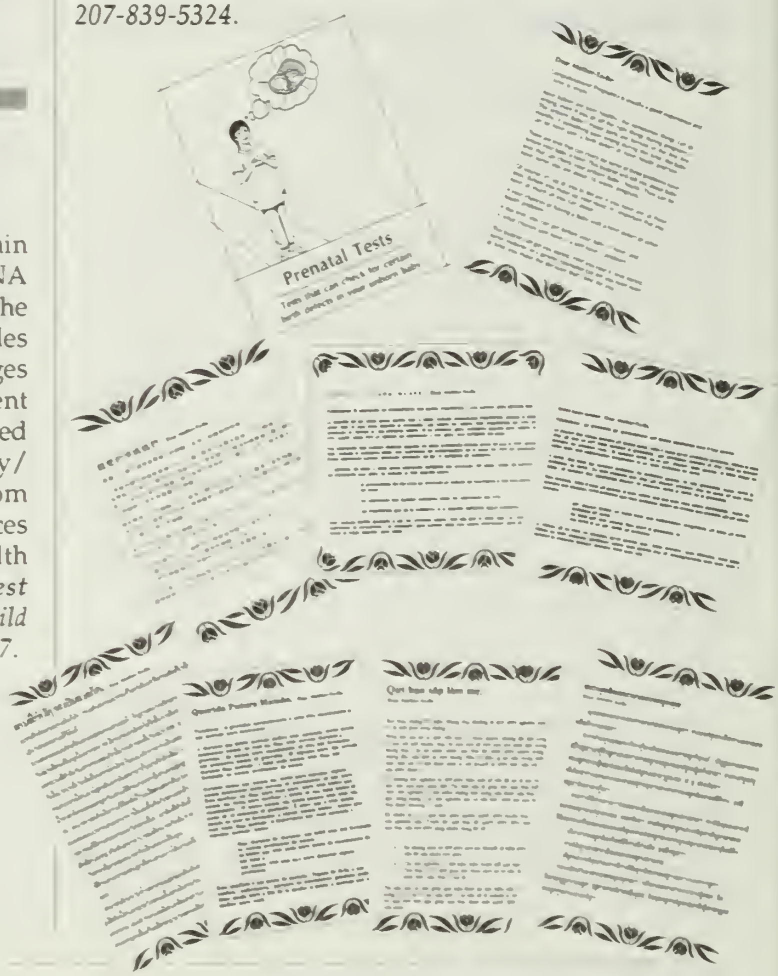
This booklet provides an up-to-date overview of cystic fibrosis and describes the genetic tests currently available. It contains information about the clinical features of cystic fibrosis, individual risk rates and carrier probabilities, and information about prenatal diagnosis, counseling issues and current treatments. This booklet was developed by The National Society of Genetic Counselors (NSGC) Cystic Fibrosis Ad Hoc Committee and endorsed by the NSGC (1990). Funding to underwrite the development of this material was provided from the Diagnostic Services Division of Collaborative Research, Inc. To assure that families make fully informed choices regarding screening for cystic fibrosis, genetic counseling is recommended prior to testing for the condition or for carrier status. ***To obtain copies of this booklet or for help in locating a genetic counselor contact:*** *The National Society of Genetic Counselors (NSGC), Executive Office, 233 Canterbury Drive, Wallingford, PA 19086, 215-8727608.*

Understanding DNA Testing: A Basic Guide for Families

This consumer-oriented booklet is designed to explain DNA analysis for families. It describes the type of DNA studies available and how testing is done, and it lists the disabilities that can be diagnosed. In addition it provides information on both the advantages and disadvantages of DNA studies. This booklet is designed to supplement counseling from health care providers. It was developed from funds provided by a grant to Emory University/ SERGG (Southeastern Regional Genetics Group) from the Maternal and Child Health Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services. ***Copies are available upon request from:*** *National Center for Education in Maternal and Child Health, 38th and R Street, N.W., Washington, D.C. 20057.*

Prenatal Tests: Multilingual Educational Booklets for Consumers

Prenatal Tests describes MSAFP screening, ultrasound, amniocentesis, pregnancy options and genetic counseling. It is written for low literacy populations and is available in Chinese, English, French, Khmer (Cambodian), Laotian, Portuguese, Spanish and Vietnamese (Haitian-Creole language version is in the process of development). English translation accompanies major headings in order to assist the provider in counseling. Information may be photocopied in whole or in part. Booklets can also be obtained for a nominal fee. Funding for these booklets was provided by the New England Regional Genetics Group (NERGG, 1989-1990) and the Massachusetts Genetics Program. Principal Investigators for the project include Robin J.R. Blatt, R.N., M.P.H., and Paula K. Haddow, M.A.T. ***To receive sample copies contact:*** *New England Regional Genetics Group (NERGG), 36 Ledge Lane, PO Box 682, Gorham, Maine, 04038-0682, 207-839-5324.*



GENETICS DIGEST

Paula K. Haddow, M.A.T.

The Genetics Digest is compiled and edited by Paula K. Haddow, Director of Education Services at the Foundation for Blood Research in Scaborough, Maine. Ms. Haddow recently joined ***The Genetic Resource*** *as Co-Editor. In addition, she serves as the Chairperson of the Education Committee of the New England Regional Genetics Group (NERGG) and of the Council for Regional Networks (CORN).*

GENETICS DIGEST SEPTEMBER 1990

National Institutes of Health Issues Report From Workshop on Population Screening for the Cystic Fibrosis Gene: The following were among the recommendations to come out of a recent NIH workshop on Population-based screening for the cystic fibrosis (CF) gene: testing should be offered to all individuals and couples with a family history of CF, but population-based screening should not be recommended for individuals and couples with a negative family history; screening should be voluntary and requires informed consent; confidentiality must be assured; providers of screening must ensure that adequate education and counseling are included in the program; educational materials should explain the hazards and benefits of choosing either to be tested or not to be tested; quality control of all aspects of the laboratory testing is required; and there should be equal access to testing ("Statement From the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene," *New England Journal of Medicine July 5*, 1990, pp. 70-71).

Researchers Use Gene Replacement Techniques to Correct the Defect in Human Cystic Fibrosis Cells in Lab Culture: Using genetically engineered viruses, researchers have inserted the normal CF gene into cultures of cells taken from the respiratory tract and the pancreas of CF patients. When the normal gene was inserted, the "sickly cells became robust, displaying such key hallmarks of biochemical normality as being able to deftly absorb and secrete chloride molecules... The ability to correct the cystic fibrosis defect in the laboratory holds great promise for treating the disease" ("Expression and characterization of the cystic fibrosis transmembrane conductance regulator," Richard J. Gregory et al, *Nature*, September 27, 1990, pp. 382-386; "Expression of cystic fibrosis transmembrane conductance regulator corrects defective chloride channel regulation in cystic fibrosis airway epithelial cells," Debra P. Rich et al, *Nature*, September 27, 1990, pp. 358-363; *The Blue Sheet*, September 26, 1990, p. 14; 'Team Cures Cells in Cystic Fibrosis by Gene Insertion" Natalie Angier, *The New York Times*, September 1, 1990, p. A1; related article that reviews progress to date in the search for a cure for CF - "New Advances Offer Cystic Fibrosis Victims Heartening Prospects," Natalie Angier, *The New York Times*, August 28, 1990, p. C3).

Mutation is Discovered for Alzheimer's Disease Amyloid Gene in Hereditary Cerebral Hemorrhage, Dutch Type: Researchers studying hereditary cerebral hemorrhage with amyloidosis of Dutch type (HCHWA-D) have discovered a cystine-to-guanine transversion, "a mutation that caused a single amino acid substitution (glutamine instead of glutamic acid) at position 22 of the amyloid protein." This mutation may be responsible for the amyloid protein buildup found in the cerebral vessel walls of patients with this disease. The protein "is similar to the amyloid protein in vessel walls and senile plaques in brains of patients with Alzheimer's disease, Down syndrome, and sporadic cerebral amyloid angiopathy" ("Mutation of the Alzheimer's Disease Amyloid Gene in Hereditary Cerebral Hemorrhage, Dutch Type," Efrat Levy et al, *Science*, June 1, 1990, pp. 1124-1126; related articles —"Platelet Coagulation Factor XIa-Inhibitor, a Form of Alzheimer Precursor Protein," Raymond P. Smith et al, *Science*, June 1, 1990, pp. 1126-1128; "Amyloid Beta Protein Precursor Gene and Hereditary Cerebral Hemorrhage with Amyloidosis (Dutch)," C. Van Broeckhoven et al, *Science*, June 1, 1990, pp. 1120-1122; "Deciphering Alzheimer's Disease: The Amyloid Precursor Protein Yields New Clues," Dennis J. Selkoe, *Science*, June 1, 1990, pp. 10581060).

Creutzfeldt-Jakob Disease Is Linked with a Gene Mutation on Chromosome 20: Researchers from the National Institute of Neurological Disorders and Stroke have reported the linkage of Creutzfeldt-Jakob disease with the scrapie amyloid precursor gene, found on chromosome 20. The scrapie amyloid precursor gene has been linked with amyloid plaques associated with Alzheimer's disease. The researchers are unsure, however, "if the mutation causes the disorder or whether a virus or second gene is required" ("Identical mutation in unrelated patients with Creutzfeldt-Jakob disease," Lev G. Goldfarb et al, *The Lancet*, July 21, 1990, pp. 174-175; "Mutation in codon 200 of scrapie amyloid protein gene in two clusters of Creutzfeldt-Jakob disease in Slovakia," Lev G. Goldfarb et al, *The Lancet*, August 25, 1990. pp. 514-515; "Mutation in codon 200 of scrapie amyloid precursor gene linked to Creutzfeldt-Jakob disease in Sephardic Jews of Libyan and nonLibyan origin," *The Lancet*, September 8, 1990, pp. 637-638; *The Blue Sheet*, September 5, 1990, p.

Mutation in Gene that Produces Collagen 2 is Linked to Some Cases of Osteoarthritis: In a worldwide study involving ten families who are affected with premature osteoarthritis, distinct defects in the collagen gene have been found in three of the family groups. In members of a family from Ohio who are part of the study, those who have premature osteoarthritis were found to have one normal gene and one defective gene for collagen 2, the predominant type of collagen in joints. A mutation that results in an arginine being replaced by a cysteine was found in one of the amino acids in the collagen molecule in these affected individuals. Researchers working on this study caution that it is not clear how many cases of this disorder might be the result of "this or other genetic defects," but they are optimistic about the possibility of specific new treatment for those cases that do result from a genetic defect ("Single base mutation in the type II procollagen gene (COL2A1) as a cause of primary osteoarthritis associated with a mild chondrodysplasia," Leena Ala-Kokko et al, *Proceedings of the National Academy of Sciences*, September, 1990, pp. 6565-6568; "Genetic Link Suggested One Form of Arthritis," Elisabeth Rosenthal, *The New York Times*, September 5, 1990).

Predisposition to Malignant Hyperthermia may be caused by Mutations in the Ryanodine Receptor Gene: Researchers in Toronto have cloned complementary DNA and genomic DNA encoding the human ryanodine receptor and mapped the ryanodine receptor gene to region q13.1 of human chromosome 19, in close proximity to genetic markers that map near the malignant hyperthermia (MH) susceptibility locus in humans. The results of these studies, along with linkage studies in families with MH indicate that "MH is likely to be caused by mutations in the ryanodine receptor gene" ("Ryanodine receptor gene is candidate for predisposition to malignant hyperthermia," David H. MacLerman et al, *Nature*, February 8, 1990, pp. 559-561; "Localizatlon of the malignant hyperthermia susceptibility locus to human chromosome 19q12- 13.2.," Tornmie V. McCarthy et al, *Nature*, February 8, 1990, pp. 562-564).

Gene for Von Recklinghausen Neurofibromatosis is Located on Chromosome 17: Two independent research teams have located on chromosome 17 the gene responsible for Von Recklinghausen neurofibromatosis ("Type 1 Neurofibromatosis Gene: Identification of a Large Transcript Disrupted in Three NF1 Patients," Margaret R. Wallace et al, *Science*, July 13, 1990, pp. 181-186; "Deletions and a Translocation Interrupt a Cloned Gene at the Neurofibromatosis Type 1 Locus," David Viskochil et al, *Cell*, July 13, 1990, pp. 187-192; "Paternal origin of new mutations in Von Recklinghausen neurofibromatosis," D. Jadayel et al, *Nature*, February 8, 1990, pp. 558-559; *The Blue Sheet*, July 18, 1990, p. 13). *The Journal of Pediatrics*, June 11, 1990, pp. 845-851 carried an article entitled "Neurofibromatosis type 1 in childhood," by Robert Listernick and Joel Charrow. The article addresses diagnostic criteria, associated problems, genetics, pathogenesis, clinical evaluation, treatment, related neurofibromatosis syndromes, and what the future holds for patients with this disorder.

Studies on First Trimester Maternal Serum Samples Confirm Trends for Down Syndrome: In a case-control study, concentrations of alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), pregnancy-specific beta 1-glycoprotein (SP1), and placental alkaline phosphatase (PALP) were measured in a set of early maternal serum samples from pregnancies that resulted in a child with Down syndrome. The results showed that the trends in the median values of AFP, uE3, and hCG were in the same direction (AFP levels and uE3 levels lower, hCG levels higher in pregnancies where the fetus has Down syndrome than in unaffected pregnancies) The authors of the study caution, however, that before it will be possible to answer the question as to whether biochemical screening for Down syndrome in the first trimester will be feasible, "it will be necessary to assemble samples from about 100 affected and several thousand unaffected pregnancies" ("First-Trimester Maternal Serum Biochemical Indicators in Down Syndrome," DJ.H. Brock et al, *Prenatal Diagnosis*, March, 1990. pp. 245- 251).

Gene for D1 Receptor is Isolated: The D1 receptor, which protrudes from the surface of cells in the brain and binds to dopamine, is thought to be defective in many diseases, including Parkinson's disease and schizophrenia. Molecular biologists have now isolated the D1 receptor gene and theorize that it works in concert with another receptor, the D2 receptor, which also binds dopamine. Recent research suggests that the D1 receptor may act to control the D2 receptor, and that this control is distorted in patients with schizophrenia and Parkinson's disease, causing an influx of dopamine. The isolation of the Dl receptor gene makes it possible for researchers to look for drugs that block the receptor dopamine in their binding to the receptor, thus offering better treatment for a variety of disorders ("Molecular cloning and expression of the gene for a human Dl dopamine receptor," Allen Dearry et al, *Nature*, September 6, 1990, pp. 72-75; "Cloning and expression of human and rat Dl dopamine receptors," Qun-Yong Zhou et al, *Nature*, September 6, 1990, pp. 76-79; "Human dopamine Dl receptor encoded by an intronless gene on chromosome 5," Roger K Sunahara et al, *Nature*, September 6, 1990, PF. 80- 83; "Cloning of human dopamine receptor," *Nature*, September 6, 1990, p. 19; "Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics," Pierre Sokoloff et al, *Nature*, September 13, 1990, pp. 146- 151; "Dominant susceptibility genes," G.M. Martin et al, *Nature*, September 13, 1990, p. 124; "Biologists Find Gene for Crucial Brain Protein"' Gina Kolata, *The New York Times*, September 11,1990, p. C3).

Adenosine Deaminase (ADA) Deficiency Gene Therapy Trial Has Begun: After months of preliminary planning, the ADA gene therapy trial began on September 14, "following approval by the Food and Drug Administration that day." In the trial, T cells were removed from a four-year old girl with ADA deficiency, a normal ADA gene was inserted into the T cells through a retroviral vector, and the altered cells were put back into the patient. '~he patient will continue to receive PEG-ADA, the only approved treatment for ADA deficiency ..." (*The Blue Sheet*, September 19,1990, p. 11; related articles - "Gene Treatments for Human Illness May Be Tried Soon" Natalie Angier, *The New York Times*, August 1, 1990, p. Al; "NIH Gene Therapy Protocol for ADA Deficiency Wins RAC Approval; Rosenberg's TIL/TNF Gene Therapy Approved," *The Blue Sheet*, August 1,1990, pp. 4,5).

Hiroshima Study Shows No Genetic Damage: An intense 40 year study of 70,000 offspring of atomic bomb survivors from Hiroshima and Nagasaki "has failed to identify an increase in congenital abnormalities, cancer, chromosome aberrations or mutational blood protein changes" ("Perinatal Loss and Neurological Abnormalities Among Children of the Atomic Bomb," James N. Yamazaki and William Schull, *Journal of the American Medical Association*, August 1, 1990, pp. 605609; "Hiroshima Study Finds No Big Genetic Change," *The New York Times*, August 1, 1990).

GENES AND CANCER

Results of the National Institutes of Health (NIH) Tumor-Infiltrating Lymphocyte (TIL)/Gene Transfer are Published: Results have been published from the NIH TIL/gene transfer trial in which marker genes were inserted into tumor-infiltrating lymphocytes that had been removed from tumors of cancer patients, and the lymphocytes were then infused back into the patient. Results of the study showed that the marker gene, which is used to identify those TIL cells that have reached the patient's tumor, switched on once the cells were re-injected into patients (5 volunteers suffering from terminal cancer) and that the technique did not harm the patients. Furthermore, the manipulated lymphocytes were not rejected by the immune system but survived in the patients for many weeks. The next move will be to insert into the tumor-infiltrating cells a gene for tumor necrosis factor, which could lend the cells extra tumor-fighting strength ("Gene Transfer Into Humans - Immunotherapy of Patients With Advanced Melanoma, Using Tumor-Infiltrating Lymphocytes Modified by Retroviral Gene Transduction," Steven A. Rosenberg et al, *The New England Journal of Medicine*, August 30, 1990, pp. 570-578; "Gene Transfer Into Humans: A First Step," *The New England Journal of Medicine*, August 30, 1990, pp. 601-603; "Foreign Genes Are Inserted In Humans, a Study Reports," Natalie Angier, *The New York Times*, August 30, 1990; *The Blue Sheet*, September 5, 1990, p. 9; "NIH Gene Therapy Protocol for ADA Deficiency Wins RAC Approval; Rosenberg's TIL/TNF Gene Therapy Approved," *The Blue Sheet*, August 1, 1990, pp.

Researchers Urge that Chemical Carcinogens be Classified on Basis of Their Damaging Effect on DNA: At present, chemical carcinogens are classified as initiators, promoters, complete carcinogens, or progressing agents. Researchers from the University of Nebraska are suggesting that "[In] light of the demonstrated ability of compounds to increase the risk of cancer by either directly altering DNA, increasing cell proliferation, or both, distinctions blur and traditional terminology is inadequate... [and that] it is useful to classify chemical carcinogens into those that interact with DNA (genotoxic) and those that do not (non-genotoxic)" ("Cell Proliferation in Carcinogenesis," S.~. Cohen and L.B. Ellwein, *Science*, August 31, 1990, pp. 1007-1111; "Too Many Rodent Carcinogens: Mutagens Increases Mutagenesis," Bruce N. Ames and Lois S. Gold, *Science*, August 31, 1990, pp. 970-971; "Chemical Carcinogens Should be Classified on Basis of Their Damaging Effect on DNA, Researchers Propose," *The Blue Sheet*, September 5, 1990, p. 8).

Research on Neurofibromatosis Leads to Possible Clues to Mechanisms in Cancer: The finding of the gene responsible for neurofibromatosis has led to an understanding of how the gene actually causes the disorder, and the discovery "strongly suggests that the protein responsible for the illness is identical or related to proteins involved in common human cancers, including tumors of the lung, liver, and brain." The protein involved may perform a tumor suppressor function and is similar to GTPase-activating protein (GAP), which is thought to play a role in the genesis of cancer ('The Neurofibromatosis Type 1 Gene Encodes a Protein Related to GAP," Gangfeng Xu et al, *Cell*, August 10, 1990, pp. 599-608; "A Stroke of Luck in Tumor Research," Natalie Angier, *The New York Times*, August 8, 1990,; "Neurofibromatosis Gene Discovery Provides Clues to Tumor Formation," *Clinical Lab Letter*, September 1, 1990, pp. 114, 115).

Positive Association is Found Between Active Cigarette Smoking and CYPlAl Gene Expression in Normal Human Lung Tissue: The major polycyclic aromatic hydrocarbon inducible-cytochrome P4501Al gene, known as CYPlAl, "normally helps liver cells tear down toxins into a harmless form that the body can easily dispose of, but ... among those in whom the gene switches on easily, it bursts to life in the lungs when pulmonary tissue is exposed to aromatic hydrocarbons, compounds found in cigarette tar and other pollutants. The gene produces an enzyme that transforms hydrocarbons into highly reactive carcinogens that damage DNA and set the stage for cancer." In the study, "17 of 19 (89%) [of] active cigarette smokers' lung tissue samples expressed CYPIAI while zero of five samples from non-smokers did ... " ("Expression of CYPAIAI Gene in Patients With Lung Cancer: Evidence for Cigarette Smoke-Induced Gene Expression in Normal Lung Tissue and for Altered Gene Regulation in Primary Pulmonary Carcinomas," T.L. McLemore et al, *Journal of the National Cancer Institute*, August 15, 1990, pp. 1333-1339: "Cigarettes Trigger Lung Cancer Gene, Researchers Find," Natalie Angier, *The New York Times*, August 21, 1990, p. C3; *The Blue Sheet*, August 29, 1990, p. 9).

K-ras Gene Mutation May Be Linked to Adenocarcinoma: A mutation in the K-ras gene "may cause some defect in the body's metabolic response to the carcinogens in tobacco smoke, thus enhancing the usual effects of these, and possibly other, carcinogens." Results of studies of adenocarcinoma of the lung, the most prevalent form of lung cancer, showed that patients whose tumor cells contain the genetic mutation are far likelier to suffer a recurrence of cancer after surgery than are those patients who do not have the mutation ("K-RAS Oncogene Activation As A Prognostic Marker in Adenocarcinoma of the Lung," Robert J.C. Slebos et al, *The New England Journal of Medicine*, August 30, 1990, pp. 561-565; "Gene Mutation Linked to Outlook in Lung Cancer Cases," Natalie Angier, *The New York Times*, September 4, 1990, p. C3; "Evidence for Mendelian Inheritance in the Pathogenesis of Lung Cancer," T.A. Sellers et al, *Journal of the National Cancer Institute*, August 1, 1990, pp. 1272-1279; "Interaction of Genes, Environment, and Life-style in Lung Cancer Development," G.E. Bonney; "Mendelian Inheritance of an Autosomal Gene May Be Linked to Lung Cancer, Study of 337 Families Finds," *The Blue Sheet*, August 8, 1990, p. 8; *The Blue Sheet*, August 29, 1990, p. 9).

National Cancer Institute Board Approves Four Year Study of Radiation-Induced Genetic Damage: The Board of Scientific Counselors of the National Cancer Institute Division of Cancer Etiology has passed a concept for a four-year study for molecular analyses of radiation-induced genetic damage, "to determine if ionizing radiation induces characteristic mutation spectra in mammalian cells different from that produced by background radiation and chemical mutagens" (*The Blue Sheet*, *July 4*, 1990, p. 4).

LEGAL/ETHICAL ISSUES

Survey of Fortune 500 Companies Shows that 12 are Currently Using Genetic Monitoring and Screening Technologies in the Workplace: Survey results released recently by the federal Office of Technology Assessment (OTA) showed that "despite 'impressive improvements' in genetic monitoring and screening technologies, only 12 Fortune 500 companies are currently using them in the workplace." A similar survey done by OTA in 1982 found that 6 companies employed such technologies (*The Blue Sheet*, October 24, 1990, p. 12).

Office of Technology Assessment (OTA) Urges Immediate Development of Standards for Forensic Applications of DNA Testing: Although forensic DNA analysis as currently performed does not produce positive identification, it has been admitted into evidence in at least 185 cases by 38 states and the U.S. military as of January 1, 1990. To date, however, "neither the federal ,government nor any state regulates DNA testing by companies or crime laboratories."

In a report issued August 5, OTA says that '~both technical and operational standards for DNA typing should be established 'at the earliest possible date"' ("DNA Testing Standards Needed for Forensic Technology: FBI may Develop National DNA Databank," *The Blue Sheet*, August 15, 1990, pp. 7,8).

Case Study of Huntington Disease is Presented in Light of Ethical Issues Involved: The May/June issue of the Hastings Center Report (pp. 31-35) carried a discussion, by an international panel of ethicists, of various ethical issues ~resented in a case study of a woman recently diagnosed with Huntington disease. The four ethicists participating in the discussion are Abbyann Lynch from the Westlunster Institute for Ethics and Human Values in London, Ontario; Andrew Czeizel from the National Institute of Hygiene in Budapest, Hungary; Francisco Salzano from the Federal University of Rio Grande do Sul, Porto Alegre, Brazil; and Kare Berg from the University of Oslo, Norway.

NIH Receives Mixed Recommendations on Continuing its Recombinant DNA Research Guidelines: The director of the Food and Drug Administration (FDA) Office of Biotechnology has suggested that the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) guidelines for research involving recombinant DNA molecules could be eliminated "in favor of other existing risk-based mechanisms of governmental oversight and regulation," such as those in a handbook written earlier by the NIH and the Centers for Disease Control. The reason for the suggestion was that "on the basis of scientific analysis, there is no rationale any longer for maintaining the guidelines purely based on a single technique." There were dissenting opinions, however, including that of the Pharmaceutical Manufacturers Association and the Robert Wood Johnson Pharmaceutical Research Institute, spokesmen for which groups urged that the RAC guidelines for research be maintained ("NIH Recombinant DNA Research Guidelines Opposed by FDA in Favor of Other Existing Regulatory Mechanisms," *The Blue Sheet*, October 17, 1990, pp. 10,

Changes are Proposed in Existing Regulations Concerning Release of Genetically Modified Organisms into the Environment: Under a new proposal the planned introduction of "organisms with hereditary traits" into the environment would be subject to federal regulation, with the scope of oversight changed for environmental release of organisms. The proposal would change existing regulations "to cover only organisms with modified hereditary traits, as opposed to all 'genetically modified organisms.'... Introduction of some genetically modified organisms 'would generally be excluded from oversight because their introduction would be similar to previous safe introductions, or because other information available regarding the risk posed by such introduction makes oversight unnecessary"'("Release of 'Organisms with Modified Hereditary Traits' Covered Under Proposed Biotech Regs," *The Blue Sheet*, September 26, 1990, pp. 9-10).

Genetically Engineered Rabies Vaccine will be Tested on a Virginia Island: A barrier island off the coast of Virginia will be the site of the first outdoor field trial of a genetically engineered rabies vaccine that was developed eight years ago. The plan for field testing has been reviewed and approved by several committees, "including one convened by the Department of Agriculture and another by the Virginia Department of Health. Both panels said the outdoor test of the vaccine posed no risk to people or animals." The site for the test, Parramore Island, "was chosen for the test because no humans live there, because it is separated from the mainland by four and a half miles of water and because it has a sizeable population of raccoons that have never been exposed to rabies" ("Rabies Vaccine to Be Tested on Virginia Island," Keith Schneider, *The New York Times*, August 14,1990, p. A17).

North Carolina Biotechnology Regulations Go Into Effect: As of July 1, 1990, "anyone planning to release genetically altered plants or microbes in North Carolina must obtain permission from the state Agriculture Department, whose professional staff will review permit applications." Final decisions on applications will be made *by* a newly established public review board, with members from the government, state, universities, public-interest groups, biotech industry researchers, and farmers, as well as the North Carolina Biotechnology Center. Although this is not considered a national model, it is seen as a stimulus for other states to do ~ "similar thorough analysis of their ability to regulate biotech" ("North Carolina Regulates Biotech," John Manuel, *Technology Review*, July 20, 1990, pp. 20-21).

Legislation is Proposed to Prevent Disclosure of Genetics Information: Legislation has been proposed that "would prevent government agencies and their contractors or grantees from disclosing genetic information about an individual without the individual's written consent." The Human Genome Privacy Act specifically covers the use of genetic information by "any executive department, military department, government corporation, government controlled corporation, government contractors, or government grantees maintaining genetic information." The legislation has not yet been introduced in the House ("Human Genome Privacy Act to Protect Federal Employees From Disclosure of Genetic Information," *The Blue Sheet*, September 19, 1990, pp. 8-9).

Food and Drug Administration is Asked to Institute Rulemaking Procedure for Genetically Engineered Products: Jeremy Rifkin, president of the Foundation on Economic Trends, has submitted a petition to the FDA asking that the agency "immediately suspend all administrative action on products manufactured through genetic engineering, including review of new products and approval of products" until the agency "completes a comprehensive rulemaking procedure to ensure the safety of genetically engineered products." The petition resulted from a recent report of a possible link "between genetic engineering and incidence of eosinophilia-myalgia syndrome which may have killed or seriously injured consumers taking the dietary supplement L-tryptophan during 1988 and 1989." Included in the petition are requests that "the FDA identify and publish a list of products manufactured by genetic engineering [and that] a public investigation be initiated on the health effects of all products approved by FDA and manufactured by genetic engineering, including public disclosure of current FDA findings in the inquiry of deaths and illnesses associated with ~ tryptophan" ("Jeremy Rifkin Seeks Ban On FDA Review of Genetically Engineered Products; Cites L-Tryptophan Reactions," *The Blue Sheet*, September 5, 1990, pp. 7-8).

MISCELLANEOUS

Gene Therapy is Included on a White House List of "Critical Technologies" : The White House Office of Science and Technology Policy has convened an expert panel that met in September to begin selecting a group of "critical technologies" that "could receive high priority for research funding in the 1990s... The panel is charged with preparing and submitting a report every two years to the President on technologies that it believes are essential for the U.S. to remain competitive with other industrialized nations." Gene therapy has been identified by the panel as an important area in health care technology, on the initial biotechnology list ("Gene Therapy, Pharmaceutical Proteins Included in Initial White House List of 'Critical Technologies'," *The Blue Sheet*, September 19, 1990, pp. 6-7).

Location for the Male Sex-Determining Gene is Proposed on the Y Chromosome: British researchers report that they have found a key gene on the Y chromosome that "is currently the best candidate for TDF," the testis determining factor in humans. The gene, which is called SRY, sex determining region Y, "was found in all the male mammals examined, including mice, pigs, chimpanzees, tigers and men" ("Additional deletion in sex-determining region of human Y chromosome resolves paradox of X,t(Y;22) female," D.C. Page et al, *Nature, July* 19,1990, pp. 279281; "Sex determination:What makes a man a man?" Anne McLaren, *Nature,* July 19, 1990, p. 216; "Scientists Say Gene On Y Chromosome Makes a Man a Man," Natalie Angier, *The New York Times*, July 19, 1990; *The Blue Sheet*, July 25, 1990, p. 10; related articles — "Population structure of the human pseudoautosomal boundary," Nathan Ellis et al, *Nature,* April 12, 1990, pp. 663-665; "The Y of Human Relationships," John Maynard Smith, *Nature,* April 12, 1990, pp. 591-592).

Genome Imprinting is Reviewed: Carmen Sapienza, in the October, 1990, issue of Scientific *American,* presents an overview of genome imprinting. The topics covered include a discussion of Mendelian genetics and how genome imprinting differs from the Mendelian rules; research that led to the realization that genome imprinting exists; a discussion of some disorders that involve or may involve imprinting; the role of imprinting in certain tumors; and the potential for further research ("Parental imprinting of Genes," Carmen Sapienza, *Scientific American,* October, 1990, pp. 52-60).

Human Genome Program Advisory Committee of the National Institutes of Health will Support Development of a Human Genome Framework Linkage Map: The NIH Program Advisory Committee on the Human Genome is encouraging the development, within two years, of a framework linkage map of the human genome to consist of "a set of highly polymorphic DNA markers spaced approximately 10 to 15 centimorgans apart." Such a map "would provide a series of highly informative landmarks that could be used to rapidly localize any new marker to a particular interval." In contrast to the framework linkage map, the longer term plan (S year!i) calls for development of a linkage map in which DNA markers are spaced two to five centimorgans apart ("Development of a Human Genome Framework Linkage Map Supported by NIH Advisory Committee," *The Blue Sheet*, June 20, 1990, pp. 5-6).

Role of the Human Genome Project in the Practice of Medicine is Presented: Scientists from the National Center for Human Genome Research writing in the Journal of the American Medical Association present a discussion of ways in which the human genome project will have an impact on the international practice of medicine. The authors discuss the potential impact of the mapping of the human genome on such diseases as Alzheimer's, arthritis, cancer, cardiovascular disease, stroke, and autoimmune disorders; and diseases such as schistosomiasis, malaria, Chagas' disease and others that plague developing countries. They also comment on the international nature of the genome research programs and the broad social implications of genome research ("The Human Genome Project and International Health," James Watson and Robert Mullan Cook-Deegan, *The Journal of the American Medical Association,* June 27, 1990, pp. 3322-3324).

Japan's Fifth Generation Computer Project is to be Used to Help Analyze Data From the Human Genome Project: Scientists from the U.S. Argonne National Laboratory and Japanese scientists will "jointly use computer systems from the Japanese fifth-generation computer project to develop techniques for handling human genome data." The fifth generation project has developed "an impressive set of hardware and software for parallel computing," and the Argonne researchers, using a high-capacity computer network link via Hawaii, will be able to access the parallel computer at the Institute of New Generation Computer Technology (ICOT) in Tokyo. Other American researchers will be able to gain access to ICOT's computers through an arrangement with Argonne ("Genome use for computer," David Swinbanks, *Nature,* June 7, 1990, pp. 466-467).

New Technology Allows Inactivation of Specific Genes in Mice: New developments in biotechnology have enabled scientists to "obliterate or modify a single gene in a mouse and so probe the role of the gene in the life of the organism." Specifically, scientists from the Whitehead Institute for Biomedical Research deactivated a beta-2 microglobulin gene and inserted the inactivated gene into mice. The researchers found that mice with the inactivated gene "possess almost no killer T-cells to fight infections...[and] the body cells of the engineered mice have no molecular markers on them to signal the immune system of their identity, as normal cells do." The technology that made this research possible "is revolutionizing biology" ("Beta2-microglobulin deficient mice lack CD4-8+ cytolytic T cells," M. Zijistra et al, *Nature,* April 19, 1990, pp. 742-746; "Gene Swap in Mice Holds Hope for Medical Gains," Natalie Angier, *The New York Times*, April 19, 1990, p. B8; "Biology Breakthrough," David Baltimore, *Technology Review*, August/September, 1990, p. 7.)

Gene Mapping Assignments Are Made by National Institutes of Health: Five universities will receive grants from the National Institutes of Health for the establishment of human genome research centers. Four of the awards are as follows:

- University of California at San Francisco, to complete a map of chromosome 4, "which is believed to contain the genes for Huntington's disease and Alzheimer's;"
- Massachusetts Institute of Technology, to "construct a detailed map of mouse chromosomes 1,11, and X and eventually create a map of the entire chromosome;"
- University of Michigan, to analyze the genes responsible for neurofibromatosis, Wilson's disease, vascular diseases and eye diseases;
- Washington University at St. Louis, genome center, to use yeast artificial chromosomes to construct complete biological maps of human chromosomes 7 and X ("Human Genome Research Center Grants Awarded by NIH," *The Blue Sheet*, October 17, 1990, pp. 5-6).

Human Gene Mapping Newsletter Makes its Debut: The first issue of the newsletter of the Human Gene Mapping Workshop Number 11 was distributed in June 1990. The aim of this newsletter is "to keep the international human gene mapping community informed about progress toward Human Gene Mapping Workshop 11 (HGMll) and to highlight particularly significant developments." This first issue includes a brief history of the HGM workshops and the goals for HGMll, together with the preparations in Oxford for HGM 10.5, and information about members of the HGMll team in the UK and about Chairs and Co-Chairs of the committees for HGMll. For more information, contact HGM Newsletter, HGMll Computing Group, Imperial Cancer Research Fund, PO Box 123, Lincoln's Inn's Fields, London WC2A 3PX, England. Telephone (44-071) 269-3629, Fax - (44-071) 430-1787.

Guppies Change Their Reproductive Behavior in an Experiment that Aids the Theory of Evolution: Scientists from the University of California at Riverside and the University of California at Santa Barbara carried out a study in which they transferred guppies from a river in Trinidad in which they were chased by a fish that-gobbled up large mature adults to a tributary of that river in which the only guppy predator was a fish that ate their young. "After 11 years and 30 to 60 generations, the investigators found that the guppies had changed exactly with the theory [that animals whose main predator attacks their young will have fewer but larger babies starting later in life, after devoting more of their energies to staying alive during that crucial period early in life, when the predator is after them], presumably based on genetic shift. The fish transferred to the tributary without the predator that ate adults had evolved to mature later and to have fewer and larger offspring" ("Experimentally induced life-history evolution in a natural population," David Reznick et al, *Nature, July* 26, 1990, pp. 357-362; "Life and times of the guppy," Brian Charlesworth, *Nature*, July 26, 1990, pp. 313-314; "Living and Dying in the Wild, Guppies Back Evolution Idea," Gina Kolata, *The New York Times*, July 26, 1990).

Items of Interest: Two magazines have recently featured articles concerning genetics. These are:

- The Genetic Age," John Carey et al, *Business Week*, May 28, 1990, pp. 68-83. This article addresses in some depth the known facts and the issues raised by genetic analysis for predicting risk for disease, gene therapy~ gene mapping, transgenics, and the technologies involved in recent breakthroughs in genetics.

- "The Telltale Gene," *Consumer Reports*, July, 1990, pp. 483-499. This in-depth look at genetic screening covers such topics as the history leading to the present ability to screen for genetic disorders, who's testing what, the ethical issues raised in testing for adult-onset disorders,potential problems with supplying the demand for services, the potential for coercion, and information about resources.

Book review: Genome: The Story of the Most Astonishing Scientific Adventure of Our Time - The Attempt to Map All the Genes in the Human Body. By Jerry E. Bishop and Michael Waldholz. New York: Simon & Schuster. Reviewed by Natalie Angier, *The New York Times*, August 12, 1990, p. 8. 'This delightful and lucid book is misleadingly named. The title "Genome" implies that it is about the human genome project ... In fact, "Genome" devotes only one chapter exclusively to the colossal enterprise... The rest of the book relays the series of scientific and medical whodunits - or howdunits - surrounding the search for the handfill of genes that cause disease. The authors follow researchers as they use the slimmest leads and the most tenuous connections to track the genes for Huntington's disease, muscular dystrophy, schizophrenia, and a host of other physical and mental miseries.... Jerry E. Bishop and Michael Waldholz, two science reporters for the Wall Street Journal, deftly capture the human motivations behind the science, and this propels their narrative inexorably forward."

GENETICS DIGEST JUNE 1990

CLINICAL

A Gene for Alcoholism? Researchers from the University of Texas, San Antonio, and the University of California at Los Angeles report finding that "the presence of the Al allele of the dopamine D2 receptor correctly classified 77% of alcoholics and its absence classified 72% of nonalcoholics" in brain cadaver tissue obtained from 35 alcoholics and 35 non-alcoholics. The researchers report that "the polymorphic pattern of this receptor gene suggests that a gene that confers susceptibility to at least one form of alcoholism is located on the q22-q23 region of chromosome 11." They caution, however, that "these findings do not imply that the dopamine D2 receptor gene probe is ready to be used as a diagnostic marker for the risk of alcoholism" ("Allelic Association of Human Dopamine D2 Receptor Gene in Alcoholism," Kenneth Blume et al, *Joumal of the American Medical Association*, April 18, 1990, pp. 2055-2060; "Finding the Gene(s) for Alcoholism," Enoch Gordis et al, *Joumal of the American Medical Association*, April 18, 1990, pp. 2094-2095; "Scientists See a Link Between Alcoholism and a Specific Gene," Lawrence K. Altman, *The New York Times*, April 18, 1990, pp. Al ff; *The Blue Sheet*, April 25, 1990, p. 10).

Follow-up Study on Babies Born with Open Spina Bifida: A cohort of 117 babies born with open spina bifida in England in the 1960s and treated within 48 hours of birth has been followed up to the present. Of the 117, 48 died before the age of 16. Of the 69 survivors, "22 were mentally handicapped, 35 were dependent on their wheelchairs, 52 were incontinent, and 12 needed anticonvulsant drugs. Seventeen had jobs" (*British Medical Journal*, February 17, 1990, p. 480; original article — "Open Spina Bifida-Outcome for a Complete Cohort Treated Unselectively and Followed into Adulthood," G.M. Hunt, *Developmental Medicine and Child Neurology*, February, 1990, pp. 108-118).

Implications of Declining Mortality from Down Syndrome: Analysis of data from Birmingham, England on the survival of babies born with Down syndrome in the years between 1942 and 1952 showed that "less than half survived the first year and only about 40" were alive at five years." More recent studies indicate an improvement in life expectancy, with "about 90% [of children born with Down syndrome] surviving to five years." This improved survival rate has many implications for service providers, including those in health, educational, and social services. The author of this editorial suggests, " ... we require more detailed information about the quality of life of Down syndrome survivors and their families in the l990s. Extending life expectancy can scarcely be regarded as a medical triumph if the effect is merely to prolong the time-scale of suffering, handicap, and dependency. Until we are more sure that the birth of a child with Down syndrome heralds a lifetime of joy and sorrow in the approximate proportions experienced by the rest of the population, we can ill afford to rest on our professional laurels" ("Declining Mortality from Down Syndrome - No Cause for Complacency," *The Lancet*, April 14, 1990, pp. 888-889).

PKU in Yemenite Jews: "The incidence of PKU varies widely across different geographic areas and is highest (about 1 in 5,000 live births) in Ireland and Western Scotland, and among Yemenite Jews. A limited number of point mutations account for most of the PKU cases in the European population." Researchers from Israel and the United States report "that a single molecular defect-a deletion spanning the third exon of the PAH [phenylalanine hydroxylase] gene-is responsible for all the cases among the Yemenite Jews" ("A Single Origin of Phenylketonuria in Yemenite Jews," Smadar Avigad et al, *Nature*, March 8, 1990, pp. 168-170.

Gene Mapped for Chronic Childhood-Onset Spinal Muscular Atrophy: Childhood-onset spinal muscular atrophy (SMA), a group of heritable degenerative diseases that "selectively affect the alpha-motor neuron, ... ranks second in frequency to cystic fibrosis among autosomal recessive disorders, and [is] the leading cause of heritable infant mortality." The disorder afflicts about one in every 10,000 babies born worldwide. Two recent studies report the mapping of the gene for type II or intermediate form and type III, or mild form "to a single locus on chromosome 5q" ("Genetic Mapping of Chronic Childhood-Onset Spinal Muscular Atrophy to Chromosome 5qll.2-13.3," L.M. Brzustowicz et al, *Nature*, April 5,1990, pp. 540-541; "Gene that Causes Spinal Disease is Isolated," Natalie Angier, *The New York Times*, April 5, 1990; Gene for Chronic Proximal Spinal Muscular Atrophies Maps to Chromosome 5q," J. Melki et al, *Nature*, April 19, 1990, pp. 767- 768).

Genetically Engineered Cystic Fibrosis Treatment Enters Clinical Trials: Genentech has filed an Investigational New Drug application with the Food and Drug Administration for its recombinant enzyme product DNase. DNase "contains a naturally occurring enzyme that breaks down DNA molecules in the mucus that accumulates in the lungs of those with cystic fibrosis." The product is human-derived and so is not expected to elicit allergic responses. Clinical trials are expected to begin sometime in July or August ("DNase Cystic Fibrosis Treatment Entering Clinical Trials: Enzyme Breaks Down DNA Molecules in Mucus," *The Blue Sheet*, May 30, 1990, pp. 7-8).

Gene for Late-Onset Alzheimer's Disease May Been Have Located: A researcher from Duke University reports that "the gene that causes late onset Alzheimer's disease may have been found on a 'proximal long arm of chromosome 19' and that 'genetic analysis ... also seems to support the linkage on chromosome 21 for the gene that causes rare early onset Alzheimer's" (*The Blue Sheet*, May 30,1990, p. 12).

Myoblast Cell Transfer Used in Children with Duchenne Muscular Dystrophy: A recent report describes the results of a study in which ...healthy myoblasts, immature muscle cells, were donated by [the father of a boy afflicted with Duchenne muscular dystrophy] and injected into [the boy's] big toe muscle." The report states that "the injected healthy myoblasts fuse with the host muscle cells, providing them with healthy genetic blueprints" and that "there were no adverse effects from the procedure and the transplanted myoblasts were not rejected. The patient was monitored for three months after undergoing the transplant" (*The Blue Sheet*, June 6, 1990, pp. 5-6).

GENES AND CANCER

Candidate Gene Found for Wilms Tumor Locus: The locus of the gene or genes involved in Wilms tumor, a common renal tumor of early childhood, has been identified as being close to a centromeric position in chromosomal band llpl3. Now a group of researchers has "isolated a candidate gene for the Wilms tumor locus in llpl3" ("Homozygous Deletion in Wilms Tumours of a Zinc-finger Gene Identified by Chromosome Jumping," Manfred Gessler et al, *Nature,* February 22, 1990, pp. 774- 778; "A Gene for Wilms Tumour?," Uta Francke, *Nature,* February 22,1990, pp. 692-694).

Can Genes Be Used as Cancer Markers? With the discovery of oncogenes (genes that can cause cancer if they are activated) and suppressor genes (genes that prevent cells from becoming cancerous), the possibility has been raised "that genes might be used as markers to help spot those people most at risk from the disease." Although much work has gone into developing 'cancer testing kits', there is still a long way to go. The problems involved in such testing include recognizing the "right" gene, the significance of linkage, accessibility to proper tissue samples, and test sensitivity. Until some of these problems are solved, the "most likely application for such tests will be in warning of the surreptitious return of a tumour after surgery, radiation treatment or drugs has apparently banished it" ("The Delphic Warnings of Cancer Genes," *The Economist,* February 17, 1990, pp. 91-92).

LEGAL AND ETHICAL ISSUES

Controversy Continues Over Screening for Cystic Fibrosis: Increasing numbers of doctors are beginning to offer a test for cystic fibrosis to all their patients in spite of the fact that the American Society of Human Genetics has "put out a statement saying that it is inappropriate to offer the test to people who do not have a family history of cystic fibrosis." The test involved "looks for a deletion that causes about 75% of all cystic fibrosis. The rest is caused by any of [at least] 31 or so other mutations or deletions, which the test does not identify." Proponents of the test say "it is better to find most people who have the defect than to withhold the test because it is imperfect," whereas opponents of offering the test to people with no family history say that "for every couple who learn they both have the defect, there will be many more who will be left worse off" ("Some Doctors Deplore Move to Test for Gene for Cystic Fibrosis," Gina Kolata, *The New York Times,* May 22, 1990.

Gene Therapy Protocol for Adenosine Deaminase (ADA) Deficiency Approved: The Recombinant DNA Advisory Committee (RAC) Human Gene Therapy Subcommittee of the National Institutes of Health (NIH) unanimously approved NIH's gene therapy protocol for ADA deficiency at its meeting on June 1, contingent on a few minor changes to the protocol. The RAC subcommittee recommended that the proposal be considered for final approval by a full committee at the NIH on June 30. Four children have been identified who are potential candidates for the new gene therapy. In the protocol, T-cells will be isolated from the patients' blood and then these cells will be infected with a special type of genetically engineered virus that includes a copy of the ADA gene that the children lack. The modified immune cells will then be returned to the children through a simple blood transfusion. "If all goes as planned, the T-cells will propagate enough of the missing enzyme [ADA] to help restore the children's immune system to normal or near-normal." In related studies, data from researchers in Milan, Italy and New York show "that when defective T-cells from children with [ADA] were injected into mice, the T-cells rapidly died. But if...the gene for the ADA enzyme [was] first inserted into the T-cells, the cells survived for months in the mouse's bloodstream." The chairman of the RAC subcommittee considered the results of this study ...the best evidence that I know of in the world that this technique may allow the T-cells to survive inside the body for a long time and carry on the normal function of the immune system" ("New Genetic Treatment Given Vote of Confidence," Natalie Angier, *The New York Times,* June 3, 1990, p. 25; "ADA Gene Therapy Protocol Clears RAC Subcommittee," *The Blue Sheet,* June 6, 1990, p. 5; related articles - "Conflict at the RAC," *Science,* April 13, 1990, p. 159; "Gene Therapy Advances," *British Medical Journal,* April 14, 1990, p. 963; "Transfer Study Expands," Diane Gershon, *Nature,* April 5,1990, p. 483).

Tumor Necrosis Factor/Human Gene Therapy Protocol Approved: The Institutional Review Board of the National Heart, Lung and Blood Institute and the NIH Institutional Biosafety Committee have approved a protocol that proposes the use of a retroviral vector to insert the tumor necrosis factor (TNF) gene into t-cells of patients with malignant melanoma. The Recombinant DNA Advisory Committee (RAC) Human Gene Therapy Subcommittee will conduct its initial review of the protocol July 30 (*The Blue Sheet,* June 13, 1990, pp. 8-9).

"DNA Fingerprinting" Situation is Reviewed: George Annas, Professor of Health Law and Director of the Law, Medicine and Ethics Program at Boston University Schools of Medicine and Public Health, has written a review of "DNA fingerprinting" in criminal cases to date. The review includes how DNA fingerprinting is used in criminal cases, how the test works, the challenges that have been made to the test, and suggestion for what should be done ("DNA Fingerprinting in the Twilight Zone," George J. Annas, *Hastings Center Report*, March/April, 1990, pp. 35-37).

Product License Application (PLA) Filed for Recombinant Factor VIII: Preliminary results of an ongoing clinical trial being conducted on the safety and efficacy of recombinant Factor VIII show that the treatment is effective and the complications are "minimal." The advantages of the product are "that it is free of hepatitis and AIDS viruses, may evoke significantly less allergic response to plasma proteins than the plasma derived or monoclonal Factor VIII, is rapidly constituted, and has the potential to be produced at a very low cost." The companies producing the product have filed product licence and establishment licence applications for It ("Recombinant Factor VIII PLA Filed by Genetics Institute, Baxter Healthcare), Complications 'Minimal'," *The Blue Sheet*, May 30, 1990, pp. 6-7).

Stanford Collecting on Patents: Since 1981, Stanford University has earned "over $17 million alone on a single three-part patent covering gene cloning techniques." The University "currently is charging companies with 75 or more employees a $50,000 sign-up fee, requires a $50,000 annual payment, and imposes a 2% royalty on end products that rely on patents held by the institution" ("Stanford Patents Pay," *Science*, March 16, 1990, p. 1298).

Genentech Wins Round on American Patent Rights for Tissue Plasminogen Activator (TPA): In April, a district court jury in Delaware ruled that three of Genentech's "key patents for the bloodclot dissolving agent tissue plasminogen activator...had been infringed." The court action "is seen as an attempt by Genentech, [which is fighting to hold on to two-thirds of the US market share], to stave off. competition" from other companies that have developed versions of TPA ("Genentech Wins Round Two," Diane Gershon, *Nature*, April 19,1990, p. 692.

Court Decision Made on Licensing Erythropoietin (EPO): For almost a year Genetics Institute and Amgen have been wrangling over rights to produce EPO by genetic engineering. In the most recent court decision regarding the issue, a judge in a U.S. district court in Boston "ordered the two companies to license to each other their respective versions of EPO, a kidney cell glycoprotein that stimulates red-blood-cell production. The agreements would be royalty-free." The order may provide a short-term solution to the conflict, but there is no assurance that one or both parties will not appeal the original patent ruling of December 11, 1989 in the federal appeals court or that either party will not claim damages for patent infringement ("Cross-licensing Ordered," Diane Gershon, *Nature*, March 22,1990, p. 278).

Criticism is Leveled at Current State of Regulations and Direction of Research in Agricultural Biotechnology: A coalition of environmental, farm, church and consumer groups in the United States has issued a report accusing agricultural biotechnology companies of "entrench(ing) and extend(ing) the pesticide era" instead of reducing the dependence of modern a~riculture on chemicals. The report's criticism was aimed at research being done by several agricultural biotechnology companies that is designed to develop crops with genetically engineered resistance to chemical pesticides ("One Man's Pesticide...," Seth Shulman, *Nature*, March 29, 1990, p. 371).

New European Rules are Approved Concerning Release of Genetically Manipulated Organisms: Environment ministers of European Communities have approved two directives that set out "strict rules for the use of genetically manipulated organisms (GMOs) in contained situations, and for environmental releases...Industrial plants will face tougher controls and must obtain explicit authorizations to work with 'high risk' (including pathogenic) GMOs." Member states have a year to implement the directives through national legislation. The directives were "opposed by leading European biotechnology companies" ("New European Release Rules Ratified," Peter Aldhous, *Nature*, March 29,1990, p. 371).

United States Leads in Patents for Genetically Engineered Pharmaceutical and Health Care Products: "United States corporations accounted for 47% of genetically engineered pharmaceutical or health care patents [in 1989], up from 1986, according to... [a] survey by the Pharmaceutical Manufacturers Association" (*The Blue Sheet*, May 2, 1990, p. 11).

MISCELLANEOUS

Research Ongoing in Genetic Components of Multi-Cause Diseases: Common diseases with complex causes are increasingly becoming the target of many molecular geneticists as researchers attempt to "untangle the diverse factors that contribute to multigene diseases." Cancer, heart disease, diabetes, high blood pressure, manic depression and schizophrenia are among the diseases that are being studied. Progress has been slow, for the most part because the most commonly used technique, RFLP linkage analysis, is far more difficult in comPlex diseases than in single gene disorders. In spite of the difficulties, researchers feel that major efforts are warranted to understand these diseases because they are "so important as public health problems and individual health tragedies" ("Dissecting the Complex Diseases," Jean Marx, *Science*, March 30,1990, pp. 1540-1542; "Complex Genetic Diseases," *Science*, March 30, 1990, p. 30; related article — "Schizophrenics' Brains," *Science*, March 30, 1990, p. 1539).

Genes that Affect Behavior Need to be Identified: Studies on human behavior have suggested that "few behaviors are controlled by single genes; instead, behaviors are often affected by several genes that in some, but not all, cases may be additive." Robert Plomin, Professor of Human Development at Pennsylvania State University, provides "an overview of the results of quantitative genetic research on behavior with a focus on the multigenetic control of behavior and the magnitude of genetic influence" and considers "the implications of these findings for the application of molecular biology techniques to the investigation of behavior." Topics included in his discussion are animal behavior, human behavior, molecular biology and behavior, and his conclusions ("The Role of Inheritance in Behavior," Robert Plomin, *Science*, April 13,1990, pp. 183-188; "Genes of Behavior," *Science*, April 13,1990, p. 123).

Attention Urged to Relationship of Environmental Mutagens to Genetic Damage: An editorial in a recent *Lancet* discusses the contribution of new mutations to occurrence of genetic disorders, the "bias toward one or other sex as the source of new mutations," offers several possible explanations for such bias, and suggests that close attention needs to be paid to "determinants of DNA vulnerability in the developing sperm and egg..." ("Origins of Genetic Disease," *The Lancet*, April 14, 1990, pp. 887-888).

Controversy Continues Over Role of Mitochondrial DNA Methods in Paleoanthropology: Mitochondrial DNA (mtDNA) studies have recently come into use as a technique for determining when and where modern man originated. Researchers from the University of California at Berkeley and from the University of Hawaii, using mtDNA studies, have developed the hypothesis (known as the "out of Africa" or "Mother of Us All" hypothesis) that "the ancestry of all modern humans can be traced to a single population-perhaps even a single woman-who lived in Africa some 200,000 years ago." Critics of the hypothesis argue that "there is no mitochondrial clock" and that "the rate of mtDNA mutation must have been affected by population extinctions in the past, moving quickly in some periods and perhaps not at all in others" ("Paleoanthropology Gets Physical," Eliot Marshall, *Science*, February 16,1990, pp. 798-801; related article — "Spontaneous Order, Evolution, and Life," M. Mitchell Waldrop, *Science*, March 30,1990, pp. 1543-1545).

DNA Brings Together Mathematicians and Biologists: The need "to understand the structure and dynamics of macromolecules and [the] need to grapple with the huge amount of data they have collected about those molecules" has brought molecular biologists "face to face with sophisticated mathematical techniques and problems in theoretical computer science. This process has taken even the biologists involved by surprise." Collaboration between experts in the two disciplines is now ongoing at several centers, including Stanford University, UCLA, the Institute for Molecular Genetics in Moscow, Western Kentucky University, Johns Hopkins School of Medicine, and the National Science Foundation-funded Program in Mathematics and Molecular Biology at Berkeley ("Mathematics Untwists the Double Helix," Barry Cipra, *Science*, February 23, 1990, pp. 913-915).

Human Genome Project is Criticized in Letter-Writing Campaign: As of the end of May, the National Institutes of Health (NIH) had received 55 letters from researchers protesting the human genome project as "mediocre science and terrible science policy." Specific criticisms include the expense of three billion dollars, the goal of sequencing plant, animal and bacterial genomes, and the drain of "talent, money and life from smaller, worthier biomedical efforts." The NIH has responded that the project "represents an important investment in the future of all biological research and is fully consonant with the mission of NIH" ("Human Genome Project Characterized as "Terrible Science Policy" in Letter-Writing Campaign to NIH," *The Blue Sheet*, May 30, 1990, p. 8; "Vast, 15 Year Effort To Decipher Genes Stirs Opposition," Natalie Angier, *The New York Times*, June 5, 1990, pp. Cl, C12).

Human Genome Organization (HUGO) Wins Grants: The International Human Genome Organization, created several years ago to "further international collaboration on the genome project," has won two grants — $350,000 from the Wellcome Trust in London for 1990, and a $1 million four year grant from the Howard Hughes Medical Institute "to cover the cost of programs and operations in the Americas office and related international activities..." ("Funds Flow to HUGO," *Science*, March 2, 1990, p. 1036; *The Blue Sheet*, May 30, 1990, p. 12).

Genetic Engineering Turns Plants Into "Factories for Medicines": By inserting human genes into plants, scientists have been able to turn the plants "into miniature factories that can produce large quantities of useful human proteins." They have grown tobacco plants that produce antibodies; potatoes that make serum albumin; rare plants that make enkephalin; and tobacco plants that make melanin. The hope is that plants will continue to be used, to make "a wide range of human hormones, growth factors, enzymes, and immune system cells" in the future ("Human Genes Turn Plants into Factories For Medicines," Sandra Blakeslee, *The New York Times*, January 16, 1990, pp. Cl, C13).

New Genes are Introduced into Food Crops: Two agricultural biotechnology companies have announced the use of genetic engineering to "improve foods" — in one case, by inserting into plants a gene that can help reduce the saturated fat in vegetable oils, and in the second case, by producing for the first time a genetically engineered coffee plant. In the case of the coffee plant, the plan is to produce coffee that is naturally low in caffeine. Although the basic work has been done, "experts say food products made from genetically engineered plants are still several years away and may face regulatory hurdles before they are approved as safe for marketing" ("2 Companies Report Gains in Gene Use to Improve Foods," Andrew Pollack, *The New York Times*, May 24, 1990).

GENETICS DIGEST APRIL 1990

CLINICAL

Prenatal and Carrier Detection of Cystic Fibrosis: Researchers from the United States and Canada have reported that they have successfully used the polymerase chain reaction (PCR) and hybridization with allele-specific oligonucleotides to analyze the presence or absence of the common CF mutation on chromosome 5, finding the mutation on 75.8% of the CF chromosomes that were examined. The study and its implications for prenatal diagnosis and heterozygote detection within families and for population based heterozygote screening are discussed in, Mutation Analysis for "heterozygote Detection and the Prenatal Diagnosis of Cystic Fibrosis," Wanda R. Lemna et al, *The New England Journal of Medicine*, February 1, 1990, pp. 291-296 (see also "PCR Test for Cystic Fibrosis Deletion," Andrea Ballabio et al, *Nature*, January 18, 1990, p.220).

Another method for prenatal diagnosis and carrier detection of CF has been reported by a group of scientists from England. They have applied the amplification refractory mutation system (ARMS) to do direct analysis of alleles of the PstI restriction length polymorphism at the KM19 locus in DNA isolated from chorionic villus biopsy and from white blood cells ("Amplification Refractory Mutation System for Prenatal Diagnosis and Carrier Assessment in Cystic Fibrosis," C.R. Newton et al, *The Lancet*, December 23/30, 1989).

Follow-up Care of Children With Sickle Cell Disease: A study done at a central London teaching hospital examined the standards of outpatient care and family care for young children with sickle cell disease. Thirty-one children between the ages of 4 months and 7 years were entered into the study with the following results: during the 12 months preceeding the study there were 93 outpatient attendances, but 13 children had not attended at least every six months, and four had not attended for more than a year; only 8 children had had three of the blood tests considered necessary for good care, and three had had none; and prophylactic treatment with penicillin and folic acid was erratic, with three children not receiving regular prophylactic penicillin. The author's conclusion is that "diagnosis of sickle cell disease on neonatal screening must be linked with follow up to ensure optimal management." ("Assessment of Care of Children with Sickle Cell Disease: Implications for Neonatal Screening Programmes, R.I.G. Milne, *British Medical Journal*, February 10, 1990, pp. 371-374).

Red, Green and Yellow Lights for Sickle Cell Disease: In a new, rapid method to detect the sickle mutation, fluorophores are coupled to the primers used in the polymerase chain reaction. The results are visible under ultraviolet light, with amplified DNA products with the normal sequence fluorescing green, those with mutant sequences fluorescing red, and heterozygous DNA fluorescing yellow ("Detection of Sickle Cell Anemia Mutation by Colour DNA Amplification," Farid F. Chehab and Yuet Wai Kan, *The Lancet*, January 6, 1990, pp. 15,16).

Malignant Hyperthermia Gene Mapped: Malignant hyperthermia (MH), which has a reported incidence of from 1 in 12,000 in children to 1 in 40,000 in adults, ... is triggered in susceptible people by all commonly used inhalational anesthetics; it is characterized by a profoundly accelerated muscle metabolism, contractures, hyperthermia and tachycardia." Researchers recently mapped the human MH locus to chromogome 19 and suggest that the skeletal muscle ryanodine receptor gene, which has been localized to the same region of chromosome 19, is "a highly likely candidate for the malignant hyperthermia susceptibility gene. " ("Localization of the Malignant Hyperthermia Susceptibility Locus to Human Chromosome l9ql2-13.2," Tommie V. McCarthy et al, *Nature*, February 8, 1990, pp. 562-563).

Retinitis Pigmentosa Mutation Found: Retinitis pigmentosa, with an incidence in the United States of about 1 in 3500 births, can occur as an autosomal dominant disorder, an autosomal recessive disorder, an X-linked disorder, or as an isolated instance. It is considered to be .". not one disease, but a group of diseases caused by mutant alleles at various loci within the human genome." Until recently, no gene defect had been described for any form of retinitis pigmentosa, but a mutation of the rhodopsin gene has now been found in a group of patients with the autosomal dominant form of this disorder. The mutation, a C-A transversion in codon 23 (corresponding to a proline-histidine substitution), "could be the cause of one form of autosomal dominant retinitis pigmentosa." ("A Point Mutation of the Rhodopsin Gene in One Form of Retinitis Pigmentosa," Thaddeus P. Dryja et al, *Nature*, January 25, 1990, pp. 364366).

Von Recklinghausen Neurofibromatosis and the Paternal Chromosome: Fourteen families were studied in which a new mutation of Von Recklinghausen neurofibromatosis (NF-l) occurred in a single individual in the second generation. In 12 of the cases ... it was highly probable that the new mutation occurred on the paternal chromosome." In the case of some other genetic disorders with a bias toward paternal origins of new mutations (e.g., hemophilia A, Lesch-Nyhan syndrome, achondroplasia) there is a marked increase in the incidence of mutations with paternal age; for NF-l, however, ... paternal age effects are slight or absent." This suggests a different mechanism of timing of germline mutation for NF " Paternal Origin of New Mutations in Von Recklinghausen Neurofibromatosis," D. Jadayel et al, *Nature*, February 8, 1990, pp. 558-561).

The Elephant Man Diagnosed: Joseph Merrick, the original Elephant Man due to his large asymmetric features with multiple skin exostoses, was posthumously diagnosed with neurofibromatosis in 1909 by Parkes Weber. This diagnosis was widely accepted until an extensive review of his physical findings and plaster casts suggested that Merrick more likely carried the diagnosis of Proteus syndrome ("The Proteus Syndrome: The Elephant Man Diagnosed," A.R. Tibbleg, *British Medical Journal*, September 13, 1986, pp. 683-685). An extensive review of Proteus syndrome, whose name is derived from the Greek god Proteus (the Old Man of the Sea), who changed shape to avoid capture, is found in "Proteus Syndrome," Curt P. Samlagka et al, *Archives* of *Dermatology*, August, 1989, pp. 1109-1114.

Alpha-l-antitrypsin Deficiency and Smoking Behavior: A follow-up study was recently done on 22 adolescents with homozygous alpha-l-antitrypsin (AAT) deficiency (detected through neonatal screening in the early 1970s) to assess liver function, lung function, and smoking behavior and attitudes. Although smoking attitudes did not differ significantly from those of control subjects, the smoking initiation rates were significantly lower than those of controls. The researchers are urging re-examination of neonatal screening for this disorder ... because augmentation therapy for adults with emphysema is now available, and screening followed by family-based smoking intervention may lead to a non-smoking life style. The latter is especially important because the current weight of epidemiologic evidence strongly suggests that in nonsmokers with this condition, severe emphysema may never develop, or, if it does, it will do so at a much later age than in smokers." ("Long Term Follow-up of a Cohort of Children with Alpha-l-antitrypsin Deficiency," Michael Wall et al, *The Journal of Pediatrics*, February, 1990, pp. 248-251).

Maternal Serum Alpha-fetoprotein Screening for Fetal Down Syndrome: A recent survey of 109 laboratories that provide screening services for a total of 586,000 pregnancies throughout the United States showed that 534,000 of these pregnancies are being provided interpretations for risk of fetal Down syndrome. Of the 96 laboratories that provide these services, 85 used a combination of maternal age and the maternal serum alpha-fetoprotein (MSAFP) value to assign risk, whereas 11 used only a fixed lower MSAFP cut-off ("Maternal Serum Alpha-fetoprotein Screening for

Fetal Down Syndrome in the United States: Results of a Survey," Glenn E. Palomaki et al, *American Journal of Obstetrics and Gynecology*, February, 1990, pp. 317-321).

Prader-Willi Syndrome: Prader-Willi syndrome (PWS), with an incidence of 1 in 25,000, is ... the most common syndromal cause of human obesity. " In fact ... " about one third of PWS patients weigh more than 200% of ideal body weight." Individuals affected with PWS also tend to have mental deficiency, the average IQ being 65, with a range from 20 to 90. "Prader-Willi Syndrome: Current Understanding of Cause and Diagnosis," by Merlin Butler, reviews... current understanding of the major clinical, cytogenetic, and DNA findings... and clinical manifestations and cytogenetic abnormalities... " associated with this condition (*American Journal* of *Medical Genetics*, 35:319-332 [1990]; see also *Genetics Digest*, February, 1990, p. 4).

Down Syndrome and Alzheimer's Disease: Results of studies of the region 21q21 to 21q22.3 of chromosome 21 in the past few years have suggested that one of the genes included in that region, the gene for the amyloid A4 protein precursor (APP),..."may contribute to Down syndrome and Alzheimer disease, accounting for the loss of mental competence characteristic to both disorders." A recent article notes, however, that ... it is becoming increasingly clear that the relationship between these two disorders is not that simple and that the postulates regarding the role of APP in both disorders need to be moderated. The initial reports of duplication of the APP gene in Alzheimer's individuals have not been confirmed, and there appears to be no linkage between familial Alzheimer's disease and restriction polymorphism of the APP gene." Nevertheless, in spite of these and other complexities, ..." the distinct possibility still remains that a contributing factor in Alzheimer's disease is in the regulation of the APP gene and that Alzheimer's disease may well share some common molecular mechanisms with Down syndrome" ("Common Ground in the Molecular Biology of Down Syndrome and Alzheimer's Disease?," James J. Greene, *Clinical Biotechnology*, January/ February 1990, pp 6-8).

Genetics in Training Programs in Obstetrics and Gynecology: In 1984 a set of educational objectives in genetics for obstetricians was developed by the Council on Resident Education in Obstetrics and Gynecology. Since that time, however, ..." clinical genetics services have continued to expand dramatically, mainly because of the increasing acceptance of genetic amniocentesis, the development of newer methods of diagnosis such as chorionic villus sampling, and the advent of both maternal serum alpha-fetoprotein screening and clinical applications of molecular biology." A review of 1237 patients referred for genetics consultation to the medical genetics center at Keesler Air Force Base showed that, as in reports from the early 198's, the most common indication for referral to a prenatal genetics clinic was advanced maternal age and evaluation for fetal chromosome abnormalities. However, in the Keesler study, the most common indications for referral excluding advanced maternal age have changed from those in the earlier studies. The study from Keesler found that after advanced maternal age, ..." the most common indications for referral are maternal serum alpha-fetoprotein screening abnormalities, familial aneuploid offspring, *a priori* risk of neural tube defects, recurrent fetal loss and multiple congenital anomalies, and mental retardation." The scientists from Keesler feel that their data identify ..." the need [in training programs for obstetricians and gynecology] for emphasis of the principles of maternal serum alpha-fetoprotein screening and DNA technologies at the resident level." ("Analysis of Indications For Referral to a Multidisciplinary Medical Genetics Clinic: Implications for Training Programs in Obstetrics and Gynecology," Allan T. Bombard et al, *American Journal of Obstetrics and Gynecology*, January, 1990, pp. 10-14).

GENES AND CANCER

Progress of Tumor Infiltrating Lymphocyte (TIL) Therapy: A team of scientists from the National Cancer Institute and the National Heart, Lung and Blood Institute has received approval from the Recombinant DNA Advisory Committee to expand the current TIL/gene transfer trial to an unlimited number of patients from the current limit of 10. In the trial, TIL cells are removed from a patient's tumor and a gene marker is inserted into the cells which are then infused back into the patient. The gene marker is used to identify those TIL cells that have reached the patient's tumor. Of the seven patients enrolled in the protocol, data are available on five, and three of these have experienced tumor regression ("TIL Therapy Shows Promise of Improved Clinical Effectiveness; Researchers Seek to Expand Trial,"*The Blue Sheet*, February 7, 1990, p.7; "NIH TIL Preliminary Trial Results Show Tumor Regression in Three of Five Patients: Trial Expanded," *The Blue Sheet*, April 4, 1990, pp. 7,8).

Gene Changes in Cancer: It is estimated that ..." as many as ten distinct mutations may have to accumulate in a cell before it becomes cancerous" Not only must DNA changes affect the cellular oncogenes, ..." activating them so that they can drive the increased cell growth and other abnormalities characteristic of cancer cells," but there must also be loss or inactivation of "two, three or even more 'suppressor genes,' which presumably work normally to inhibit cell growth." To date, researchers have found alterations in the RAS oncogene in colon cancer, a missing or defective retinoblastoma gene in small-cell carcinomas of the lung, and deletions of specific segments" of chromosomes 17 in lung and breast cancers, 3 and 11 in lung cancers, 5 and 18 in colon cancers. "The tumor suppressor genes appear to be one of nature's successful approaches to protection against cancer; thus, they may be a rich resource for clinical anticancer therapies." However, much more needs to understood about these genes and their mutations before such clinical use can be made of the findings ("Many Gene Changes Found in Cancer," Jean Marx, *Science*, December 15, 1989, pp. 1386-1388; "Tumor Suppressor Genes," Ruth Levy Guyer, *Science*, December 15, 1989, p. 1367). A thorough review of the subject of tumor suppressor genes appears in "Tumor Suppressor Genes: The Puzzle and the Promise,' by Ruth Sager, Science, December 15, 1989, pp. 1406-1411.

Tumor Suppressor Gene in Human Colorectal Cancer Identified: "Colorectal cancer is rapidly becoming the most extensively characterized human malignancy in terms of the molecular genetic alterations associated with its progression." The recent isolation and identification of a tumor suppressor gene (termed DCC for deleted in colorectal carcinomas) on chromosome 18q21-qter is a major new finding, and further study of this gene "may provide new insights concerning the molecular mechanisms governing colorectal neoplasia, particularly regarding the roles that cell-surface interactions play in controlling abnormal cellular proliferation" ("Identifying Tumor Suppressor Genes in Human Colorectal Cancer," Eric J. Stanbridge, *Science*, January 5, 1990, pp. 12,13; "Colorectal Cancer Genes," Ellen Solomon, *Nature*, February 1, 1990, original article-"Identification of a Chromosome 18q Gene that is Altered in Colorectal Cancers," Eric R. Fearon et al, *Science*, January 5, 1990, pp. 49-55).

DNA Markers for Familial Adenomatous Polyposis Identified on Both Sides of the Gene: DNA markers have been identified that "closely flank" the locus of the gene causing familial adenomatous polyposis (FAP), on chromosome 5. FAP is an autosomal recessive disorder that predisposes to colorectal adenocarcinoma: the discovery of the bridging DNA markers..."will allow prenatal and presymptomatic diagnosis of FAP, with more than 99.9% reliability in the majority of families, by means of already available markers. " ("Presymptomatic Diagnosis of Familial Adenomatous Polyposis by Bridging DNA Markers," C.M.J. Tops et al, *The Lancet*, December 7, 1989, pp. 1361-1363).

Interferon Gene Deletions Identified in Acute Lymphoblastic Leukemia: Researchers from the University of Chicago have reported the results of a study showing that ..."deletions of the interferon genes are relatively frequent in primary leukemia cells from patients with [acute lymphoblastic leukemia (ALL)] (29%), and that approximately half these deletions are submicroscopic." The researchers ..."propose that the loss of a leukemia suppressor gene, either one of the interferon-alpha genes or an unrelated but closely linked gene, may be the relevant genetic defect in these deletions, and that this defect may be associated with the leukemogenic process in ALL." ("Deletions of Interferon Genes in Acute Lymphoblastic Leukemia," Manuel 0. Diaz et al, *The New England Journal of Medicine*, January 11, 1990, pp. 77-82).

LEGAL AND ETHICAL ISSUES

Issues Involved in Carrier Screening for Cystic Fibrosis: The recent identification of the cystic fibrosis (CF) gene has led to many questions about widespread CF carrier screening, which, if the entire United States population were to be screened, would apply to between 100 and 200 million people. Some of the concern arises from the fact that, ..".at present, the CF test can identify only a single mutation in the CF gene present in 70-75% of Caucasian carriers. Other CF cases are caused by an unknown number of rare mutations." As a result, the test would identify only about half the couples at risk of having a child with CF. Many genetics professionals feel that even when the remaining mutations associated with CF have been identified, there will still be issues to be resolved, such as who should be screened and when? at what age? who will educate the public about the test beforehand and explain the results? In addition, there are the issues of confidentiality, informed consent, quality control of laboratory testing, and equal access. Some experts are recommending that widespread CF screening ..."should be able to detect mutations in the gene with 90-95% accuracy before the test is used in the general population" and that, meanwhile, pilot programs be developed to examine methods of testing and educating large numbers of people ("Cystic Fibrosis Screening Accuracy Should

Reach 95% Before Widespread Use of Test, Panel Recommends," *The Blue Sheet*, March 7, 1990, pp. 9,10; "To Test or Not to Test," Leslie Roberts, *Science*, January 5, 1990, pp. 17-19; "Screening for Cystic Fibrosis," Harvey R. Colten, *The New England Journal of Medicine*, February 1, 1990, pp. 328-329; "Cystic Fibrosis: Prospects for Screening and Therapy," *The Lancet*, January 13, 1990, pp. 79-80; "Identification of the Cystic Fibrosis Gene," Richard A. Knight and Margaret E. Hodson, *British Medical Journal*, February 10, 1990, pp. 345-346; "Screening for Cystic Fibrosis," P.J. Roderick and J. Chapple, *The Lancet*, December 9, 1989, pp. 1403-1404).

Redefining Recombinant DNA: The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) has announced plans to hold five public hearings on revising the definition of recombinant DNA. Committee members have suggested that the definition be broadened to "encompass newer techniques in molecular genetics." ("TIL Therapy Shows Promise of Improved Clinical Effectiveness; Researchers Seek to Expand Trial," *The Blue Sheet*, February 7, 1990, p. 7).

Preliminary Approval for First Attempt at Gene Therapy: The NIH Recombinant DNA Human Gene Therapy Subcommittee of the Recombinant DNA Advisory Committee (RAC) has heard and given preliminary approval to a gene therapy protocol for adenosine deaminase (ADA) deficiency. The protocol involves taking blood from the patient, isolating the T-cells, growing them in vast quantities in the laboratory, and inserting a retroviral vector that has been genetically altered to carry the ADA gene. "The T-cells are then reinserted into the subject and should begin to produce normal ADA genes. The therapy would treat children with severe combined immune deficiency who are ADA deficient." The subcommittee has asked to see, before their next meeting in June, additional data on the protocol, including an external review of the effectiveness of PEG-ADA, a new enzyme replacement product for treatment of ADA deficiency, as an alternative therapy. The proposal must win the approval of several other review boards as well as that of the Food and Drug Administration (FDA) and the director of the NIH before human trials can proceed (Gene Implant Therapy Is Backed For Children With Rare Disease), Natalie Angier, *The New York Times*, March 8, 1990, p. Al; "Gene Therapy Moves A Step Closer to Reality," George Johnson, *The New York Times*, March 11, 1990; "NIH TIL Preliminary Trial Results Show Tumor Regression in Three of Five Patients; Trial Expanded, "*The Blue Sheet*, April 4, 1990, pp. 7,8).

Future Use of Gene Therapy: The National Institute of Allergies and Infectious Diseases (NIAID), an Institute of the National Institutes of Health, has released a draft report stating that "the perfection of therapies using genes and gene products will be one long-term goal [for NIAID] for the 1990s and beyond." In addition, the report says that "support is also needed for replacement therapy with gene products. The task force points out that replacement of missing enzymes, antibodies and cytokines is being done, but except in the case of blood serum antibodies, to only a very limited extent'. "('Therapies Using Genes and Gene Products to be High Priority in 1990'8, NIAID Task Force Predicts, "*The Blue Sheet*, January 24, 1990, p. 5).

Maine Case Challenges Use of DNA Fingerprinting: In a pretrial hearing in Portland, Maine, to "determine whether evidence from DNA-typing is 'sufficiently reliable to be held relevant' as evidence, the prosecution abandoned its case after a series of blunders were revealed under cross-examination." The case involved the sexual molestation of a five-year-old girl, and the prosecution had DNA fingerprint evidence that.". a semen sample ... found at the scene of the crime matched a blood specimen from the defendant." The DNA evidence was dropped and the charges against the defendant subsequently withdrawn because of a problem with the way the laboratory that performed the DNA testing had tried to correct for ..." a phenomenon known as bandshifting that, according to one expert, arises in perhaps 30% of DNA fingerprinting cases." In addition, there were ..." some irregularities in the way the data were handled. For example, an autoradiograph was mislabeled and an independent check was not done to confirm the result of one probe." One expert suggests that the laboratory's ..." attempt to correct bandshifting in the [Maine] case represents the premature introduction of the technique into a forensic case," suggesting that "[t]he right place to address these questions is in scientific journals rather than in courtrooms. This is an extremely powerful technology, but there has got to be a better way to ensure that it is used properly."("Maine Case Deals Blow to DNA Fingerprinting," Colin Norman, *Science*, December 22, 1989, pp. 1556-1558; "DNA and the Law," *The Lancet*, February 17, 1990, pp. 381-382; "DNA Fingerprinting on Trial," Alan Andersen, *Nature*, December 21/28, 1989, p. 844).

The National Academy of Science has announced that it has received funding and approval to carry out a 14 month study on DNA technology in forensic science. The panel, chaired by Victor McKusick, was due to have its first meeting in January. Financial support in the amount of $250,000 has come from the Federal Bureau of Investigation (FBI), the

National Institute of Justice, the National Science Foundation (NSF), the National Institutes of Health (NIH), and the Sloan Foundation ("DNA Fingerprinting on Trial," Alun Andersen, *Nature*, December 21/28, 1989, p. 844).

Legal Implications of Employer Use of Genetic Screening: The mapping of the human genome raises the potential for misuse of information arising from genetic screening, as in the case of an employer wanting to test his/her employees for risk of developing certain diseases. However, because issues analogous to those raised by genetic testing have already been raised by employer testing for communicable diseases, "[a]pplicable law already exists ... for the issue of genetic testing by employers to identify those at risk of disease." The Americans with Disabilities Act (Disabilities Act), which waspassed by Congress and signed into law by the president this year, will "restrict employers from using tests for genetic risk of disease," and will also "forbid the use of medical tests to detect disabilities in employees, unless the testing would provide information about the person's ability to perform job-related functions." A provision in the Act "that will prohibit discrimination against those who are perceived as being disabled as well as against those who are actually disabled" is expected to be interpreted as providing protection for persons with a risk of genetic disease ("Genetic Screening by Employers," David Orentlicher, *Journal of the American Medical Association*, February 16, 1990, pp. 1005-1006) .

Ethical Use of Gene Transfer: A discussion of the ethical use of gene transfer is presented in "Genetics and Human Malleability," by W. French Anderson, in the *Hastings Center Report* for January/February, 1990, pp. 21-24. Making the point that "gene transfer should be used only for the treatment of serious disease and not for putative improvements," the author discusses what can be done, what will be possible to do, and what should be done.

The Biotechnology Business: Two American companies, Genetics Institute and Amgen, are still wrangling over rights to produce erythropoietin (EPO) by genetic engineering. A recent court decision ruling "validates the central claims of the patents held by the two companies but at the same time doubles the confusion by considering both patents partially invalid and mutually infringing." One of the companies involved, Genetics Institute, has not yet received FDA approval and is manufacturing EPO in Japan in collaboration with a Japanese Company "which uses the same host cell for which Amgen received a patent." Amgen's recombinant EPO gained FDA approval last year. In another development, House members are introducing a bill that "would close a legal loophole that allows foreign companies to make biotechnology products using components patented in the United States without getting permission from the patent holders and to sell the products without paying royalties." Genetics Institute claims that if the bill were approved, ..." it could not import EPO from Japan..." ("Court Battle Ends at the Start," Diane Gershon, *Nature*, December 21/28, 1989, p. 846; "Biotech Protection," *Science*, February 16, 1990, p. 811).

Genentech Merger Raises Questions: The Swiss-based "multinational health-care conglomerate" Roche Holdings Ltd. announced in February that it would purchase a 60% stake in Genentech, Inc., "the largest US biotechnology company." This development, which "took the world by surprise" has led to some question about the lengthy process required in the United States for FDA approval of new drugs, especially "when the materials on trial are intended to be identical with those produced naturally in normal human beings." ("Swiss Company Takes a Stake in Genentech," Diane Gershon, *Nature*, February 8, 1990, p. 495; "Biotechnology Eclipsed?," *Nature*, February 8, 1990, p 494).

MISCELLANEOUS

1989's Major Scientific Development: In the opinion of the journal *Science*, the polymerase chain reaction (PCR) was "the major scientific development of 1989, " and the journal "has chosen as its first 'Molecule of the Year' the DNA polymerase molecule that drives the reaction." One of the first uses of this technology "led to improved diagnosis of... sickle cell anemia, because the PCR technique depended on much less clinical material than standard procedures ... PCR can also be used to amplify trace amounts of genetic material of infectious agents in blood, cells, water, food, and other clinical and environmental samples." PCR-based tests are also used for such varied purposes as detecting pathogens that are difficult or impossible to culture, for cancer diagnosis and research, for forensic, missing person, and paternity cases, for facilitating matches of transplant donors and recipients, and for archaeological research. Its future uses include replacing gene cloning as the amplification method of choice for gene sequencing ("The Molecule of the Year," Ruth Levy Guyer and Daniel E. Koshland, Jr., *Science*, December 22, 1989, pp. 1543-1546).

"The Polymerase Chain Reaction," Barry I. Eisenstein, *The New England Journal of Medicine*, January 18, 1990, pp. 178-181, discusses the background of the development of this method, the method itself, research applications, and specific applications in medicine.

The Human Genome Project: In response to a request from Congress that the Human Genome Organization (HUGO) develop a plan to "outline an 'optimal strategy' for achieving scientific, information, administrative and ethical goals during the project's first five years," HUGO has drafted a five-year plan. The draft is now awaiting the signature of James Watkins, Secretary of Energy. The Administration is proposing that the National Institutes of Health be allocated $108 million for the genome project for FY '91 and that the Department of Energy be allocated another $47 million for its share of the project ("Human Genome Five-Year Plan Release is 'Imminent' NIH Advisory Council Official Tells Biotech Meeting," *The Blue Sheet*, April 4, 1990, pp. 6,7).

"James Watson and the Search for Biology's Holy Grail," by Stephen S. Hall, in *Smithsonian*, February, 1990, pp. 41-48, describes the human genome initiative and chronicles the career of James Watson and his role as coordinator of the NIH genome project. In 1987, the National Research Council "called for an immediate effort to develop a genetic linkage map as the first goal of the genome project." Although every major report on the project has reiterated that goal, the feasibility of accomplishing it in 3 to 5 years, as originally planned, is in question. In the three years since the National Research Council called for an immediate effort, "the map is not that much further along," and one researcher has said that "[there is zero probability that we will develop a 1-centimorgan [genetic] map unless there is a major change in policy." The NIH advisory committee on the genome project has set up a new working group to examine options and has scaled back the goal for the map. For the next five years the goal will be a map in which the averaga distance between markers in 2 centimorgans (rather than 1), with no gap greater than 5 centimorgans ("Whatever Happened to the Genetic Map?," Leslie Roberts, *Science*, January 19, 1990, pp.281,282).

Human Genome Newsletter to be Published: The Department of Energy and the Human Genome Office plan to publish, starting in mid-April, a joint, bi-monthly newsletter, *Human Genome News*, covering news about human genome research. The publication will include information on sequencing of the human genome and some model organisms, as well as research news and grant announcements. For information on receiving this newsletter, contact the Human Management Information System, Oakridge National Lab, P.O. Box 2008, Oakridge, TN 37831-6050.

Genetic Sequence Data Bank Online: The Genetic Sequence Data Bank (GenBank), a collaborative effort involving the National Institute of General Medical Sciences, IntelliGenetics, Inc., the National Library of Medicine, the Department of Energy, and the Los Alamos National Laboratory, "provides a computer data base of all known DNA and RNA sequences and related biological and bibliographic information." It currently contains about 30 million nucleotides in approximately 26,000 different entries in biological material and organisms ranging from viruses to humans, and most of the entries include information on which organism, tissue or cell the nucleotide was taken from; which regions of the genome it is mapped to; and its location relative to neighboring known sequences, along with annotations covering the functional role of gene segments such as protein coding regions ("Genetic Data Base Service" James P. Swyers, *Research Resources Reporter*, December, 1989, pp. 13,14).

DNA Fingerprinting and Paternity Testing: As reported in the February, 1990 issue of this *Digest*, DNA fingerprinting is coming into use for determining paternity. A recent article in *Obstetrics and Gynecology* discusses the use of this technique for determining the paternity of a fetus, using DNA obtained from amniocytes or chorionic villi. The authors state that ..."[t]he simplicity, speed, reliability, and accuracy of molecular genetic analysis make it ideally suited to address questions of familial relationship in the prenatal period" ("Prenatal Determinations of Paternity by Molecular Genetic 'Fingerprinting,' " Bruce W. Rovacs et al, *Obstetrics and Gynecology*, March 1990, pp. 474-478).

BOOK REVIEWS

Prenatal Diagnosis in Obstetric Practice. Ed. MJ Whittle, JM Connor. Oxford: Blackwell Scientific, 1989. Reviewed by J. P. Calvert in the *British Medical Journal*, January 27, 1990. "It is unusual to read a textbook that fulfills its stated aims as completely as does this one-the authors are to be congratulated. It is written for obstetricians to bring them up to date with the rapid advances in prenatal diagnosis and to provide a comprehensive source of references to the almost 400 conditions that can be diagnosed."

Genetics: The Clash Between the New Genetics and Human Values. David Suzuki and Peter Knudtson. Cambridge, MA: Harvard University Press, 1989. Reviewed by Richard C. Hermann in the *Journal of the American Medical Association,* January 5, 1990. This book presents a primer of fundamental genetics; details the basic concepts of molecular, cellular, and population genetics; describes the modern revolution in genetic engineering; and explores the ethical issues generated by modern genetics. Although the book is written for lay readers, ..."[m]any physicians could benefit from the material" The authors .". have written an excellent book that, if widely read, will provide much of the technical education and ethical sensitization needed to broaden public debate."

GENETICS DIGEST FEBRUARY 1990

CLINICAL

Cystic Fibrosis: With the announcement in August that researchers had identified the gene responsible for most cases of cystic fibrosis (CF) (see *Genetics Digest,* December 1989. p. 1), the race to develop a screening test to detect carriers of the gene began. Many in the medical community have expressed 'serious reservations' about widespread screening before the identification of additional mutations (the new test can detect only 70% of CF carriers). Other concerns are "that resources are not available for providing counseling services on the scale required for routine widespread carrier screening for CF " and that there is a "lack of mechanisms to ensure that [laboratory] standards are maintained." The American Society of Human Genetics has established a working group to study these and other issues raised by the new test and plans to produce a report this year (*"CF Screening Premature?." Christine McGoulty. *Nature,* November 23. 1989. p. 334: *"CF Screen: Still Too Soon," R. Weiss, *Science News,* November 18, 1989. p. 325; *"The Cystic Fibrosis Gene is Cloned!." *Hospital Practice,* November 15, 1989. pp. 177-178: **"Carrier Screening in CF," Leo Ten Kate, *Nature,* November 9 . 1989 . p. 131) .

Mapping Chromosome 21: Chromosome 21 has only 1,000 to 1,500 of the 100,000 human genes, and about 10% of genes on this chromosome have been identified. These include the gene that instructs the body to make the enzyme superoxide dismutase, which appears to control connections between certain nerves and muscles and also appears to control blood levels of serotonin; the gene for the amyloid protein found deposited outside of nerve cells in the brains of Alzheimers patients; two potential cancer-causing genes; a gene that encodes information for making the lens of the eye; and a gene involved in the synthesis of purine, excess levels of which are found in some people with mental retardation (*"Understanding Down Syndrome: A Chromosome Holds the Key." Gina Kolata. *The New York Times,* December 5. 1989. p. C3).

Manic Depressive Disease: A paper published in 1987 claimed that manic depression in a large Amish pedigree was linked to two marker genes on the short arm of chromosome 11. Further studies have, however, "markedly reduce[d] the probability of linkage between bipolar affective disorder and the Harvey- ras-l oncogene and insulin loci on chromosome 11." The reasons for the original conclusions and subsequent reversal are explained in "False Start on Manic Depression." by Miranda Robertson. in *Nature,* November 16, 1989, p. 222 (**). Although the particular linkage described in 1987 now appears unlikely, the updated studies "still indicate manic depression has some sort of genetic basis...It may involve more than one gene or a single gene on another chromosome" (**"Re-evaluation of the Linkage Relationship Between Chromosome 11p Loci and the Gene for Bipolar Affective Disorder in the Old Order Amish." John R. Kelsoe, et al. *Nature,* November 16. 1989. pp. 238-243: *"Manic Depression: Suspect Gene Acquitted." A. McKenzie, *Science News.* November 18. 1989. p. 327: *"Scientists Now Doubt They Found Faulty Gene Linked to Mental Illness," Harold M. Schmeck. *The New York Times,* November 7. I989. p. C3).

Schizophrenia: A European group, the European Science Foundation (ESF) in 1986 launched a network to "establish a European database on pedigrees, to foster international collaboration, to create cell lines from patients and their families, and above all to work out common criteria for the diagnosis of schizophrenia," a plan that "could lead to an identification of the genetic loci associated with the disease within five years." However, two major reservations about the "methodology and management of the scheme" have surfaced. The first is that "funding bodies are likely to be unwilling to release funds to the scheme only for the ESF to pass it on to research groups it already supports, and the second is that the extent to which "the ESF would wish to dictate terms to laboratories participating in the scheme is unclear" (*"ESF Scheme Criticized." Henry Gee. *Nature*, November 9. 1989. p. 110).

Obesity: Scientists at the American Heart Association's scientific sessions in November presented research suggesting that "obesity follows a classic model of recessive inheritance," with an estimated 5% of the population having inherited a tendency toward obesity. The researchers stress that these individuals "can minimize their weight gain by altering environmental risk factors such as diet or a sedentary life style" and say that further studies are needed "to clarify the interaction between environmental and genetic factors in the development of obesity" (*"Family Ties Point to Recessive Obesity Gene, " K. A. Fackelmann. *Science News*. November 18. 1989).

Sickle Cell Disease: Recent advances in sickle cell research may have produced a "turning point in [the] battle against the hereditary disease, which afflicts millions of people around the world." The multi-pronged attack on the disease in recent years has included the following results: "at several centers doctors have begun a clinical trial of the drug hydroxyurea which increases the body's production of a type of hemoglobin that resists sickling; new drugs are being tested that interfere with the structure of sickle cell hemoglobin, blocking it from becoming inflexible: calcium channel blockers, drugs used to treat cardiovascular disease, have shown some promise in reducing the rigidity of sickled cells in early human tests; several chemicals are under investigation that affect blood cell surface membranes and blood vessel linings. Researchers hope they will lead to ways to interfere with vessel clogging; scientists say they are completing development of a genetically altered mouse that could be used in research and serve as the first true animal model for the disease" (*"Scientists Cite Gains in Sickle Cell Disease," Warren E. Leary. *The New York Times*, November 28, 1989. pp. C1,.C6.)

According to a study published recently, children with sickle cell anemia "may also suffer significant neuropsychological deficits...Researchers find that children inheriting the red blood cell disorder have lower IQs and more learning disabilities than do their siblings without the disease-perhaps as a result of brain damage during their first few years of life" (*"Brain Risk Seen in Sickle Cell Kids." R. Weiss, *Science News*. December 23 and 30, 1989, p. 404: original article-***"Neuropsychologic Impairment in Children With Sickle Cell Anemia." Andrea V. Swift et al. *Pediatrics*, December, 1989. pp. 1077-1085).

Gene Therapy: Early interest in gene therapy, centered around the stem cells of bone marrow as the logical place to start, for a number of reasons, including the permanence of the genetic repair and the fact that "once the stem cell has a normal gene, all its progeny will too." In fact, however, stem cells have been difficult for a variety of reasons. They are "hard to get hold of in any quantity - they are very rare and difficult to infect with retroviruses..." Efforts now are being directed at "selectively turning certain lymphocytes, endothelial cells, and other types of accessible cells into what amount to *in vivo* drug delivery systems by splicing into them genes that code for specific proteins." One disorder that is being looked at closely for this type of "genetic drug" therapy is alpha-1 antitrypsin deficiency; an autosomal recessive disorder that usually leads to emphysema early in life. Researchers at the National Heart, Blood, and Lung Institute are studying the possibility of putting the gene for alpha-l antitrypsin into an aerosol that could be sprayed into the lungs of people with emphysema, thereby providing them with a "genetic shield" of protective levels of alpha-l. " As promising as these projects are, however, they still face some difficult technical and regulatory hurdles" (**"Designing Cells to Deliver Drugs." Barbara J. Culliton. *Science*, November 10. 1989. p. 746: *"Gene Replacement Therapy for Hereditary Emphysema?," Andrew Skolnick. *Journal of the American Medical Association*, November 10, 1989, p. 2499; **" A Genetic Shield to Prevent Emphysema?" Barbara J. Culliton. *Science*, November 10. 1989, pp. 750, 751: related articles — *"Edging Towards Human Gene Therapy," Peter Newmark, *Nature*, November 16, 1698, p. 221; *"Preliminary Results May Open Door to Gene Therapy Just a Bit Wider," Charles Marwick, *Journal of The American Medical* Association. October 13, 1989, p. 1909 *"French Anderson's 20-Year Crusade," *Science*, November 10, 1989, p. 748).

GENES AND CANCER

More on Nobel Prize for Oncogene Work: In the December, 1989, issue of this *Digest*, several articles were cited on the awarding of the Nobel Prize in Physiology or Medicine to J. Michael Bishop and Harold Varmus for their discovery that the oncogenes of animal tumor viruses are derived from cellular genes. Good summaries of their work appeared in *Nature* (**"Nobel for Oncogenes," Peter Newmark. October 12, 1989, p. 475) and in the *Journal of the American Medical Association* (*"Short-circuiting Oncogenes May Become Basis of New Cancer Therapies," Beverly Merz, November 24, 1989. p 2785).

The Oncogene and Lung Cancer: Results of many studies suggest that the normal p53 gene, located on the short arm of chromosome 17 (the portion of chromosome 17 that is frequently deleted in human tumors), acts as an anti-oncogene (a tumor suppressor gene). This theory was further strengthened by a recent study that identified p53 abnormalities in 17 of 30 (57%) lung cancer cell lines, representing all histological types of cancer. An additional 17% (5/30) expressed very low levels of p53 mRNA. "These findings. coupled with the previous demonstration of 17p allele loss in lung cancer, strongly implicate p53 as an anti-oncogene whose disruption is involved in the pathogenesis of human lung cancer" (**"p53: A Frequent Target for Genetic Abnormalities in Lung Cancer," Takashi Takahashi et al, *Science*, October 27, 1989, pp. 491-494)

More on p53: As mentioned above, the gene p53 is located on the short arm of chromosome 17 (17p) and, in human tumors, the short arm of chromosome 17 is often deleted. To determine whether tumors"with allelic deletions of chromosome 17p contain mutant p53 genes in the allele that is retained," researchers analyzed p53 sequences of 19 tumors with single chromosome p53 alleles. The tumors were derived from the breast, lung, brain, colon or mesenchyme. They were able to demonstrate mutant p53 genes in all but three of the tumors, a finding that "suggests[s] that p53 mutations play a role in the development of many common human malignancies" (***"Mutations in the p53 Gene Occur in Diverse Human Tumour- Types," Janice M. Nigro et al. *Nature*, December 7, 1989, pp. 705-708).

Growth and Regulation of Cells: A model of how cell growth regulation can be explored and defined is presented in "Oncogenes. Growth Factors and Signal Transduction," Brian Druker et al.,*The New England Journal of Medicine*, November 16. 1989. pp. 1383-1391 (***). Topics include oncogenes and oncoproteins, mechanisms of signal transduction, phosphotyrosine and antiphosphotyrosine antibodies, identification of two substrates of tyrosine kinase growth factors, a candidate phosphatidylinositol kinase, and the *c-raf* protein kinase and signal transduction.

LEGAL AND ETHICAL ISSUES

The Big Picture: A four day European meeting was held in October of 1989 on the subject of genetic heritage and human rights. During the meeting workshops were held on a variety of subjects including research on the human genome and its implications, predictive medicine, *in vitro* fertilization, and biotechnology. Recommendations from the workshops dealt with, among other topics, the psychological dangers of screening for diseases that occur only later in life, genetic fingerprinting, the need to conserve genetic diversity through gene banks, and the existing dangers of eugenic choices. A summary of the workshops and their recommendations is due to be published soon (*"Ethical Matters," Peter Coles, *Nature*, November 9, 1989, p. 108).

DNA Fingerprinting: Articles on DNA fingerprinting have been appearing in law literature, and three of these have recently come to our attention. The first, "Method and Applications of DNA Fingerprinting: A Guide for the NonScientist," by K.F. Kelly et al (***Climinal Law Review* February, 1987, pp. 105-110), describes the scientific background of the technique "in terms which, it is hoped, will be comprehensible to the non-scientist and which will make clear its forensic and legal importance." The author also discusses the accuracy of identifications made using DNA fingerprinting and areas of possible application. The second article, "DNA 'Fingerprinting' Advanced as Identification Technique," in *DNA Criminal Practice Manual*, September 23 1987, defines DNA fingerprinting, presents the advantages of the technique, describes the British experience, and discusses the legal implications of the process. The third article is "DNA Fingerprinting and Proof of Paternity," by David B. Jackson (***The Family Law Reporter*, May 16, 1989, pp. 3007-3013). The intent of this article is "to clarify the DNA fingerprinting process in the context of paternity testing. so that its usefulness may be more effectively and accurately resolved." The author explains the molecular biology involved, the testing technique, and how the test results are used in court cases involving paternity. This article also contains a selected bibliography.

Human Genome: The ethics working committee of the human genome advisory committee has recommended that beginning in 1991, "town meetings be held throughout the United States to inform the general public about the human genome initiative and to solicit opinions on the ethical, social and legal issues it raises." The National Institutes of Health (NIH) and the Department of Energy (DOE) foresee these meetings as a means of anticipating and avoiding such problems as loss of employment or insurance for people who are diagnosed as having genetic disorders in the interim phase in the genome project when genetic diseases can be detected but not treated (*"Public Debates on Ethics." Christine McGourty, *Nature*, December 7. 1989. p. 603).

Biotechnology: A German biotechnology company has been ordered by a West German court to "cease construction of a nearly completed plant that would use genetically engineered bacteria to make human insulin." The plant would use *E. coli* to produce human insulin "as United States companies have been doing for a decade." Opponents to the plant feel, however, that all genetic engineering is hazardous. The decision is seen as increasing the pressure on the government to pass a law regulating genetic engineering in factories and laboratories (*"New Law is Overdue," Steven Dickman. *Nature*, November 16, 1989, p. 218; see also *Genetics Digest*, December 1989 issue, p. 4, "Licensing Battle in West Germany").

Biotechnology Regulation: A draft recommendation from the Administrative Conference of the United States "calls for continuation of interagency coordination [of federal regulation of biotechnology] under the auspices of the White House Office of Science and Technology Policy." The Administrative Conference, which is charged with evaluating administrative law and recommending changes to federal agencies, noted that "public acceptance of agency decisions is especially important ...because of the novelty and uncertainty of the risks associated with biotechnology" and recommended that agencies "adopt appropriate measures to allow public participation" and that agencies "seek ways to make biosafety information available to the public to the maximum extent consistent with protection of the proprietary interests of subminers of confidential business information" (*"New Legislation to Regulate Biotechnology is Unnecessary, U.S. Administrative Conference Concludes." *The Blue Sheet*, November 15. 1989. pp. 6,7).

MISCELLANEOUS

Prader-Willi Syndrome and Genetic Imprinting: Research over the last few years has shown that 60% of cases of Prader-Willi syndrome have a deletion of part of the chromosome 15 contributed by the father; the maternally contributed chromosome 15 is intact. In about 40% of Prader-Willi cases, however, no such chromosomal deletion is found. Scientists have now discovered that in two cases in which no deletions in chromosome 15s were found, each patient had two different chromosome 15s derived from the mother; i.e., there was total absence of a paternal chromosome 15 in both cases. The researchers have concluded from this "that a gene or genes in the region 15q11q13 must be inherited from each parent for normal human development" (**"Genetic Imprinting Suggested by Maternal Heterodisomy in Nondeletion Prader-Willi Syndrome," Robert D. Nicholls et al., *Nature*, November 16, 1989. pp. 281-284; "Prader Lacks Fader: Angelman Misses Mom?" R. Weiss, *Science News*, November 18, 1989, p. 324).

The Human Genome Project: Some of the recent articles on this project include:

> "Three Human Genome Research Centers will be Funded by NIH in FY 1990: Watson Favors Large Centers," *The Blue Sheet*, November 15, 1989, pp. 3,4. James Watson, Director of the National Center for Human Genome Research at the National Institutes of Health (NIH) has announced that NIH is establishing three human genome research centers in FY '90. The "initial activities of the centers will include the genome sequencing of a model organism, the production of a physical map of the human chromosome and the development of a specific technology." Watson also emphasized the importance of the interface between scientific laboratories and the private sector, especially companies that manufacture machines for DNA sequencing. (See also *"Plan for Genome Centers Sparks a Controversy," Leslie Roberts, *Science.*, October 13, 1989, pp. 204-205).
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> "Promising New Technique May Accelerate Genome Mapping," Beverly Merz, *Journal of the American Medical Association* , November 3, 1989, p. 2353. A new technique that uses "landmarks called sequence tagged sites (STSs)" may speed up the genome mapping process. The procedure would enable investigators to identify newly mapped genes by having access to the sequences of a unique track of DNA contained within [a specific clone]. Because the tracks are only 200 to 500 base pairs long they can be readily sequenced and their identities entered into a data base for access by interested parties... The principal utility of these DNA tracks, known as sequence-tagged sites..., is that they can be used to rewrite all existing chromosomal maps." (See also *"Gene Mappers Meet on Strategy," Joseph Palca, *Science*, September 8, 1989, p. 1036; "Human Genome Project," *Science*, September 29, 2989, p. 1431: "A Common Language for Physical Mapping of the Human Genome," Maynard Olson et al,

Science, September 29. 2989, pp. 1434-1435: **"New Game Plan for Genome Mapping." Leslie Roberts, *Science*,. September 29, 1989, pp. 1438-1440).

"NIH/DOE Human Genome Project Should Focus on Higher Resolution Maps of Fewer Chromosomes," *The Blue Sheet*, December 13, 1989, pp. 3,4. The Program Advisory Committee on the Genome Project met recently to consider a draft five year plan jointly prepared by the National Institutes of Health (NIH) and the Department of Energy (DOE). The document, which is to be presented to Congress, "will lay out the optimal strategy for achieving 'scientific information', administrative and ethical goals during the project's first five years." One plan, which suggests completion of "a fully connected human genetic map with markers spaced at an average of one centimorgan apart," has raised doubts on the part of at least one investigator who feels that 'there is zero probability that we will develop a one centimorgan map unless there is a quick and major change in policy in this area."

"DNA Discoverer James Watson now Dreams of Curing Genetic Disease," *Journal of the American Medical Association*, December 15, 1989, pp. 3340-3344. This article summarizes James Watson's accomplishments to date and offers his plan for the human genome project.

*"Technology, Cost, Cooperation, Ethics Challenges Face Genome Mapping Plan," Charles Marwick, *Journal of the American Medical Association*, December 15, 1989, p. 3247. A number of major hurdles face the genome mapping project "before it can move into high gear," including "developing technology to enable the project to go forward at reasonable cost; encouraging other nations to contribute to the estimated total $3 billion bill; and considering ethical and legal implications that will flow from the results of the project." (See also *"Diplomacy Please." *Nature*, November 2, 1989, pp. 1,2.)

"Sequences and Consequences of the Human Genome," Daniel E. Koshland, Jr., *Science*, October 13, 1989, p. 189. "Sequencing the human genome puts us on the threshold of great new benefits and some real but avoidable risks. There are immoralities of commission that we must avoid. But there is also the immorality of omission - the failure to apply a great new technology to aid the poor, the infirm, and the underprivileged. We must step boldly and confidently across the threshold."

"Johns Hopkins as International Host," Christine McGourty, *Nature*, November 23, 1989, p. 330. A new database will be established at Johns Hopkins University as part of an international network of databases "to support the mapping and sequencing of the human genome." The new data base will "provide access to primary data and literature citations, and daily updates of information generated by scientific workshops, the database's scientific editors, and individual laboratories...Users will also have access to ... the on-line version of Mendelian Inheritance in Man, Victor McKusick's classic encyclopaedia of human genetic diseases." London will be the site of the second centre in the network. (See also *"Dealing With the Data," Christine McGourty, *Nature*, November 9, 1989, p. 108.)

"Japan Boosts Genome Research," Leslie Roberts, *Science*, October 27, 1989, pp. 439-440. The human genome program in Japan, as now envisioned, will focus on five areas including genetic and physical mapping and chromosome analysis; the construction of high quality complementary DNA (cDNA) libraries for specific tissues; innovative DNA sequencing technologies; efforts to improve existing databases and to devise new software for genome analysis; and obtaining the maps and sequences of model organisms, such as nematode, *Drosophila*, or certain plant species.

Genes and Immunity: Scientists from the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology have discovered a gene that is believed to play an important role in the recombination process by which the body generates a wide array of protective antibodies. Although they do not yet know the exact function of the gene which they have named RAG-I, for recombination activating gene, the researchers "suspect that it might encode a recombinase that reshuffles antibody genes" ("Key Gene in Immune Defenses is Believed Found," Harold M. Schmeck, *The New York Times*, December 22, 1989; "Antibody Scrabble: Two Genetic Players Proposed," A. McKenzie, *Science News*, January 6, 1990. p.4: **"Scientists Discover 'Master Gene' for Immune System," *Clinical Lab Letter*, February 1, 1990, p. 1; original articles — "The V(D)J Recombination Activating Gene, RAG-I," D.G. Schatz et al, *Cell*, December 22, 1989, pp. 1035-1048; **"Making Antigen-Receptor Genes," Gary Rathbun et al, *Nature*, December 21/

28, 1989, p. 863; "A Protein Binding to the Jk Recombination Sequence of Immunoglobulin Genes Contains a Sequence Related to the Integrase Motif," Norisada Matsunami et al, *Nature*, December 21/28, 1989, pp. 934-937).

Genetically Engineered Vaccines for Respiratory Syncytial Virus (RSV) and Group A Streptococcus? Approximately 2,000 infants die each year from RSV, and an attempt during the 1960s "to induce immunity with a formalin-inactivated whole virus vaccine was disastrous." Recently, however, researchers have produced a genetically engineered glycoprotein that "can be used to induce an immune response against both of the RSV [immunogenic] glycoproteins." The product has not been tested in humans, but in challenge tests with cotton rats "a very small amount of the [engineered] protein completely protected the rats from RSV infection." Studies in primates will go on this year, with clinical trials expected to follow within the year. Meanwhile, scientists from Oregon and New York have used recombinant DNA technology "to splice genetic information from the streptococcus bacterium into a carrier vaccinia virus...The resulting vaccine ... provid[es] immunity to various infecting serotypes." Although vaccinia virus would probably not be used as a vector in the United States "because of safety concerns," it has not been ruled out completely in developing countries such as India where "an estimated 6 million children have rheumatic heart disease" ("New Vaccines for Respiratory Tract Ills? Genetic Engineering Pursues These Goals," Marsha F. Goldsmith, *Journal of the American Medical Association*, October 20, 1989, p. 2055).

Prenatal Diagnosis:

> "Blood Test for Pregnant Women Appears to Reveal Sex of a Fetus," Gina Kolata. *The New York Times*, December 21. 1989, pp. A1, B19. Original article — **Prenatal Sex Determination by DNA Amplification from Maternal Peripheral Blood," Y. M. D. Lo et al. *The Lancet*, December 9, 1989, pp. 1363-1364. In the first "wholly successful effort to determine the sex of a fetus by analyzing a blood sample of a pregnant woman," a new, "exquisitely sensitive test," polymerase chain reaction, was used to find Y chromosome genes in the blood of the pregnant women. Researchers found the genes in 12 of the 19 women tested, and those twelve women gave birth to boys. The other women, whose blood contained no genes from the Y chromosome, gave birth to girls.
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> "Early Prenatal Diagnosis." *British Medical Journal* November 11, 1989. pp. 1211-1213. This article discusses the uses, advantages, and risks of various prenatal diagnostic techniques, including chorionic villus biopsy, amniocentesis, ultrasound studies, and cordocentesis.

DNA Techniques in Medicine: Two articles in recent issues of the *British Medical Journal* under the heading Scientific Tools in Medicine, present techniques for the study of DNA. The first. **"Blotting Techniques for the Study of DNA, RNA, and Proteins" by Peter C. Hayes et al., discusses the general principle behind the blotting methods, southern and northern blotting methods, western blotting, problems and future development. The second article. **"Principles of DNA Cloning." by John S. Miles et al. discusses what DNA cloning is, the types of recombinant DNA libraries and the use of cloned DNA probes in medical genetics.

Expression of Modified Genes in Mice: A new technique has been developed "to introduce altered genes into mouse embryos so that, when the mice mature, some of them pass a functioning copy of the gene to their offspring." The importance of this achievement lies in the opportunity it affords researchers to study the expression of the altered gene over long periods of time in many animals offspring ("New Technique Allows Study of Altered Genes in Offspring," Sandra Blakeslee, *The New York Times*, November 14. 1989. p. C3: "Altered Genes Inserted in Germ Line." Ruth Levy Guyer, *Science*, November 10. 1989, p. 731: original article — "Germ-Line Transmission of a c-ab1 Mutation Produced by Targeted Gene Disruption in ES Cells." Pamela L. Scwartzenberg et al. *Science*,. November 10. 1989, pp. 799-803.

'Maleness Gene': Studies reported in 1987 suggested that maleness was determined by a gene designated as ZFY, on the Y chromosome. This hypothesis arose from studies involving males that had two X chromosomes and a tiny portion of a Y. It appeared at that time that the piece of the Y chromosome always contained the ZFY gene. In new studies, however some males have been found who do not have the ZFY gene. These results "again raise the question of what genetic information determines maleness'" (*"Scientists Dismiss Finding of 'Maleness' Gene," Gina Kolata, *The New York Times*, January 2, 1990. original article — **"Genetic Evidence that ZFY is Not the Testis-Determining Factor," M.S. Palmer et al, *Nature*, December 21/28, 1989: related articles - **"Testicular Differentiating Factor: Current Concepts." Barbara C. McGillivray. *Growth*, December 1989. pp. 1-3; ***"Putative Transcription Activator with Alternative Isoforms Encoded by Human ZFX Gene." Ansbert Schneider-Gadicke et al, *Nature*, December 7, 1989, pp. 708-711).

Mitochondrial DNA: A review of what is known about the role of mitochondrial dysfunction in the origin of certain diseases is presented in "Mitochondrial DNA: Small, Beautiful and Essential." by L.A. Grivell, *Nature.*, October 19, 1989. pp. 569-570 (***).

Animals as a Future Source of Human Hemoglobin: Functional human hemoglobin has been successfully produced in transgenic mice, and research is now going on to apply the same techniques to allow porcine or bovine production of human hemoglobin in larger quantities. "The advance could eventually lead to a 'safe alternative' to human hemoglobin from donors," and some scientists are predicting that genetically engineered hemoglobin could be tested in humans within the next two years (*"Could Animals Be a Future Source of Human Hemoglobin?," *Clinical Lab Letter*, January 1, 1990, pp. 5.6).

Help for Black Rhinos: The endangered black rhinoceros may be saved from extinction by the discovery of genetic similarities of groups of black rhinos from different countries. Until recently, the groups had been classified as separate subspecies and therefore were kept apart to preserve the genetic diversity, but recent studies on blood samples collected from the various groups showed that "the two main groups of black rhinos had similar gene pools that can be mixed." This finding allows the combining of isolated populations of the animals into "rhino sanctuaries" to increase breeding rates and afford protection from poachers (*"Einks May Help Save Rhinos From Extinction," *The New York Times*, October 31, 1989).

DNA and Elephant Tusks: Scientists may have come up with a way to distinguish between illicit ivory poached from endangered elephant herds in areas of Africa north of Zimbabwe and ivory obtained from elephants legitimately culled from well managed herds in the southern part of Africa. After DNA fingerprinting and isotope analyses were used on tusks from the different elephant populations the question was asked whether either technique could reveal any features of the DNA that could reliably be used to discriminate tusks from the different populations. One of the scientists working on the project replied that DNA fingerprinting "differentiates between Kenya and Tanzania. It's what we've been looking for, and I'm sure we'll find more." Meanwhile, other scientists are using a new approach to restriction mapping in an attempt to identify animals from different herds (**"Science Gives Ivory a Sense of Identity," Jeremy
Cherfas, *Science*, December 1, 1989, pp. 1120-1121).

Mapping the Plant Genome: As plans progress for mapping the human genome, plant scientists are proposing similar efforts for the plant genome. The United States Department of Agriculture has established an office to start plans for a 10-year, $500 million program to study the genes "that control traits like drought resistance and nutrient use in economically important plants." The proposed project would not attempt to chart all the DNA in one plant, but rather would focus on gene systems or traits, such as growth, heat tolerance, or moisture content, and see how those things are regulated by genes in several different plants (*"Genetic Maps May Point the Way to Healthier and Sturdier Crops," Warren E. Leary, *The New York Times*, January 9, 1990, p. C4).

BOOK REVIEWS

Cystic Fibrosis. Edited by Peter Goodfellow. Oxford University Press: 1989. Pp.96 Pbk $26.95.
The Fragile X Syndrome. Edited by Kay E. Davies. Oxford University Press: 1989. Pp. 138. Pbk $24.95.

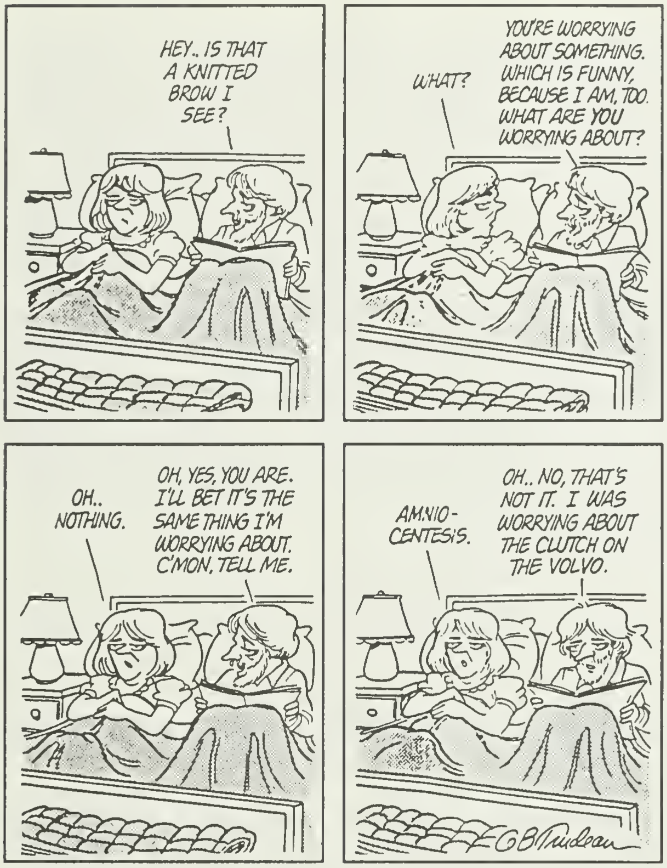
These books are the first in a new series. "Molecular Medicine," published by Oxford University Press, were reviewed for Nature by Ann Harris and Martin Bobrow of the Division of Medical and Molecular Genetics, United Medical and Dental Schools of Guy's and St. Thomas's Hospitals, London. The reviewers conclude that "the format and pricing of these books make them accessible to a wide audience of students, and to both scientists and clinicians, each of whom is likely to learn something from the other's point of view" ("Two Diseases." *Nature,* October 19, 1989,p. 580).

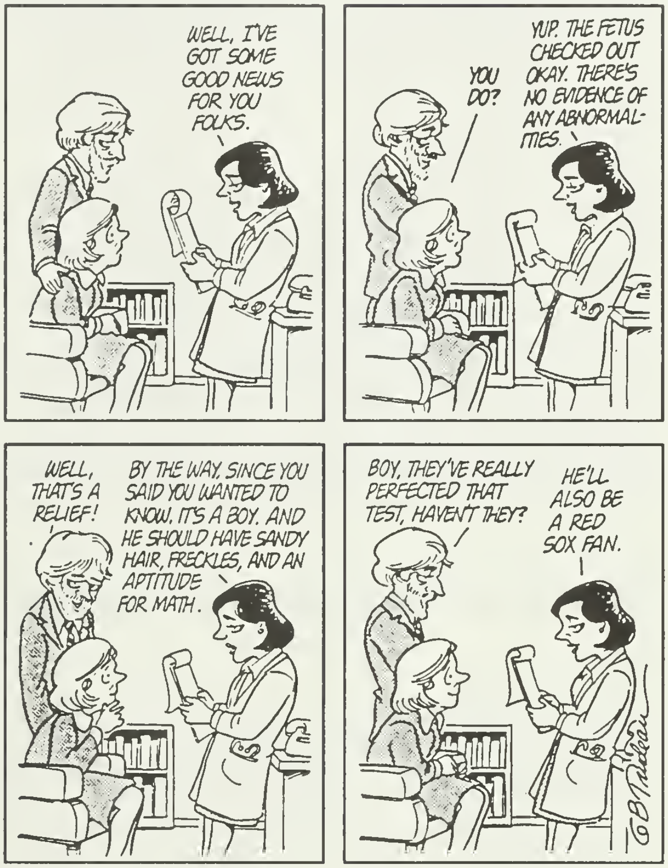
*Please Note: The information in the Genetics Digest is derived from sources believed to be reliable. However , neither the **The Genetic Resource** or The Foundation for Blood Research are responsible for the absolute correctness or sufficiency of the information. Articles may be coded for difficulty from *(least difficult) to ***(Most difficult).*

IN THE MEDIA

Are you aware of the content of comics, articles, and books on genetics which appear in the popular press? Media attention to human genetics is increasing dramatically in an effort to keep the public informed of new developments. This column selectively reprints or summarizes such information. The material is contributed by our readers as well as by the Editors. Please send current information of interest for inclusion in this column to ***The Genetic Resource****.*

FUNNIES?


HEY.. IS THAT A KNITTED BROW I SEE?
WHAT?
YOU'RE WORRYING ABOUT SOMETHING. WHICH IS FUNNY, BECAUSE I AM, TOO. WHAT ARE YOU WORRYING ABOUT?
OH.. NOTHING.
OH, YES, YOU ARE. I'LL BET IT'S THE SAME THING I'M WORRYING ABOUT. C'MON, TELL ME.
AMNIO-CENTESIS.
OH.. NO, THAT'S NOT IT. I WAS WORRYING ABOUT THE CLUTCH ON THE VOLVO.
GBTrudeau


WELL, I'VE GOT SOME GOOD NEWS FOR YOU FOLKS.
YOU DO?
YUP. THE FETUS CHECKED OUT OKAY. THERE'S NO EVIDENCE OF ANY ABNORMALITIES.
WELL, THAT'S A RELIEF!
BY THE WAY, SINCE YOU SAID YOU WANTED TO KNOW, IT'S A BOY. AND HE SHOULD HAVE SANDY HAIR, FRECKLES, AND AN APTITUDE FOR MATH.
BOY, THEY'VE REALLY PERFECTED THAT TEST, HAVEN'T THEY?
HE'LL ALSO BE A RED SOX FAN.
GBTrudeau

Contributed by Kathryn Spitzer-Kim, M.S. • Prenatal Diagnostic Center, Inc. • Lexington, Massachusetts

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PAST ISSUES

The Genetic Resource

Volume 1

Number 1: Maternal Serum Alpha-Fetoprotein Screening: Some Practical Advice for Physicians *(Haddow)* ❖ Alpha-Fetoprotein Test Kits: Withdrawal of Proposed Rules *(Federal Register Excerpts)* ❖ FDA Withdrawal of Proposed Rules Covering Alpha-Fetoprotein Test Kits: A Commentary *(Haddow)* ❖ Establishing a Diagnosis of Neurofibromatosis and Tuberous Sclerosis: A Review Article *(Traynor)* ❖ The Pregnancy Environmental Hotline *(Bartoshesky)* ❖ Other News: Diabetes in Early Pregnancy Study *(Holmes)* ❖ Massachusetts Department of Public Health: Genetic Counseling Services *(Blatt & Green)* ❖ Directory of Comprehensive Genetic Centers. 1984: 16 pages.

Number 2: Chorionic Villus Sampling *(Miller)* ❖ Molecular Approaches to Prenatal Diagnosis of Genetic Disease *(Amos)* ❖ Can Second Trimester Maternal Serum Alpha-Fetoprotein (MSAFP) Measurements be Used to Screen for Down Syndrome?*(Haddow)* ❖ The Reproductive Outcome Surveillance System (ROSS)*(Katz)* ❖ Evaluation of Spontaneous Abortion and of the Malformed Fetus, Stillbirth and Deceased Newborn: A Practical Approach for Health Care Workers *(Bieber)* ❖ Agent Orange and Birth Defects*(Bartoshesky)* ❖ Directory of Comprehensive Genetic Centers. 1984: 16 pages.

Volume 2

Number 1: Maternal Phenlyketonuria (PKU): The Unexpected Challenge *(Barnico & Cullinane)* ❖ Variant Forms of Tay-Sachs Disease Identified by Carrier Testing *(Kolodny)* ❖ The Fragile X Syndrome *(Meryash)* ❖ Smoking in Pregnancy: A New Approach to Solving a Continuing Problem*(Haddow)* ❖ Alcohol and Pregnancy: Prevention of Adverse Outcomes*(Weiner & Rosett)* ❖ The New England Regional Genetics Group *(Henderson)*. 1985: 16 pages.

Number 2: Emotional Aspects of Infertility: A Public Health Concern *(Griffin)* ❖ Maternal Serum Alpha-Fetoprotein (MSAFP) Screening in Massachusetts: An Update *(Miller)* ❖ Massachusetts Spina Bifida Association: An Advocacy Group's Perspective on MSAFP Screening*(Anderson)* ❖ Assuring Quality in the Performance of MSAFP Screening *(Haddow)* ❖ Low MSAFP and Down Syndrome: Information for Physicians *(Ad Hoc Committee, New England Regional Genetics Group)* ❖ Quality Control in MSAFP Screening*(Knight)* ❖ New England Regional Genetics Group Update *(Henderson)* ❖ Legislative Update*(Dievler)* ❖ Vaccinations during Pregnancy*(Rosenwasser, O'Brien & Feingold)* ❖ What Are Your Clients Reading?*(Blatt)* ❖ An Updated Directory of Comprehensive Genetic Centers within Massachusetts. 1985/1986: 47 pages.

Volume 3

Number 1: Genetic Screening: An Overview *(Reilly)* ❖ Carrier Screening for Sickle Cell Anemia *(Mahmoud, Blatt, Miller)* ❖ Carrier Screening for Thalassemia *(Berman, Crocker, Fosburg, Sallan)* ❖ Carrier Screening for Tay-Sachs Disease: Revised Guidelines *(Kolodny)* ❖ Application of Gene Probes in Prenatal and Carrier Testing *(Boehm)* ❖ The Massachusetts Newborn Screening Program *(Levy)* ❖ Newborn Screening for Toxoplasmosis *(Hoff)* ❖ Congenital Toxoplasmosis: A Parent's Experience *(Burton, Sundman)* ❖ Tuberous Sclerosis: An Advocacy Groups' Perspective *(Connors)* ❖ Legislative Update: Newborn Screening for Tuberous Sclerosis *(Mailloux)* ❖ Teratogen Exposure Registry and Surveillance (TERAS) *(Bieber)* ❖ Lab Notes: MSAFP Screening Update *(Reid)*. ❖ A Directory of Comprehensive Genetic Centers within Massachusetts.
1986: 56 pages.

Number 2: A Referral Guide to Genetic Services and Decision Making and Support Organizations in Massachusetts ❖ Genetic Counseling Centers ❖ Pregnancy Counseling Centers ❖ Private Educators and Counselors ❖ Religious Counselors &Pastoral /Counseling Services ❖ Pregnancy Information and Referral Services ❖ Advocacy and Support Groups for Persons with Specific Disorders ❖ Organizations for Persons With Special Needs ❖ Special Needs Adoption Services ❖ Infertility Counseling & Referral Services ❖ Infertility Clinics ❖ Alternative Fertilization Programs ❖ Artificial Insemination by Donor ❖ Adoption Information & Referral ❖ Support Groups for Pregnancy Loss ❖ Alternatives to Abortion ❖ Pregnancy Termination Services ❖ Pregnancy Termination Support Groups ❖ March of Dimes Birth Defects Foundations ❖ State Government Agencies ❖ Translation Services. 1987: 46 pages.

Volume 4

Number 1: Prenatal and Carrier Testing by DNA Analysis *(Boehm)* ❖ Prenatal Diagnosis of Cystic Fibrosis *(Amos & Janes)* ❖ Prenatal Diagnosis of Duchenne Muscular Dystrophy *(Tantravahi, Hawley, Speer, & Latt)* ❖ Genetic Linkage Test for Huntington's Disease *(Meyers)* ❖ How New Technology Becomes Routine Procedure: The Case of DNA-Based Tests for Genetic Disorders *(Holtzman & Hewitt)* ❖ DNA Diagnostic Testing: Laboratory Service Issues *(Simon)* ❖ What's Next? The Promise of Gene Therapy *(Excerpted from the New Human Genetics)* ❖ General Resources *(Blatt)* ❖ Genetic Counseling Services within Massachusetts.
1987: 46 pages.

Number 2: An Overview of Embryologic and Fetal Development *(Pescitelli)* ❖ Documented Teratogens *(Excerpted from an ACOG Technical Bulletin)* ❖ Decision-making About Reproducitve Hazards *(Welch)* ❖ In Utero Exposure to Lead: Sources, Assessment and Sequelae *(Bellinger & Matthews)* ❖ State Surveillance of Birth Defects and Other Adverse Reproductive Outcomes *(Adapted from a DHHS Report)* ❖ Massachusetts Congenital Anomaly Surveillance *(Lanes)* ❖ Slone Epidemiology Unit Birth Defects Study *(Mitchell)* ❖ Brigham and Women's Hospital Malformations Surveillance Program *(Holmes)* ❖ Teratogen Exposure Registry and Surveillance *(Bieber)* ❖ Prospective Epidemiological Study of Neural Tube Defects and Other Congenital Anomalies *(Milunsky)* ❖ Environmental Health Institute *(Bloom)* ❖ Massachusetts Teratogen Information Service *(O'Brien, Rosenwasser, & Lennon)* ❖ Massachusetts Right-To-Know*(Dinan)* ❖ General Resources *(Blatt)* ❖ Genetic Counseling Services within Massachusetts. 1988: 44 pages.

Volume 5

Number 1: Genetic Mutations: Mechanisms and Identification *(Wagner)* ❖ The Genetics of Common Disorders: Cancer *(Spatz)* ❖ Coronary Artery Disease *(Mahoney)* ❖ Neurological and Behavioral Conditions *(Housman)* ❖ HLA-Associated Diseases *(Mahoney)* ❖ Impact of Presymptomatic Tests on Physician Practice *(Reilly)* ❖ General Resources *(Blatt)* ❖ Genetics Digest *(Haddow)* ❖ Genetic Counseling Centers in Massachusetts.
1989: 64 page.

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Past issues of The Genetic Resource are available at a nominal cost. For more information contact:

The Genetic Resource
Massachusetts Genetics Program
Massachusetts Department of Public Health
150 Tremont Street, 2nd Floor
Boston, MA 02111
TEL: (617) 727-5121 • FAX: (617) 723-1659

Attn: Robin J.R. Blatt

-Genetic Counseling Centers in New England-

CT CT CT

State Genetics Program

Connecticut Statewide Genetic Services
University of Connecticut Health Center
Connecticut State Department of Health Services
150 Washington Street Avenue
Hartford, CT 06032

Contact: Gretchen Landenburger, M.S.
Phone: 203-566-3287
Services: Coordination and Funding of Statewide Genetic Services and Activities, Information and Referral on Clinical Genetics, Newborn Screening, Sickle Cell Disease, Community Trait Screening, Maternal PKU, and Human Genetics Education.

University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030

Department of Pediatrics
Division of Human Genetics

Director:	Robert Greenstein, M.D.
Phone:	203-679-1501
Gen. Counselors:	Sharon Langshur, M.S.- Pediatrics 203-679-1500 Leslie Ciarleglio, M.S. - Prenatal Diagnosis 203-679-1501 Glenda Spivey, M.S. (Pregnancy Exposure - Risk Line) 203-679-1502 or 800-325-5391
Services:	Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, Prenatal Diagnosis, Pregnancy Exposure - Risk line, Prader-Willi Clinic, Neurogenetics Clinic, Craniofacial Disorders Clinic.
Outreach Sites:	Waterbury, Norwich.

Yale University Medical School
333 Cedar Street
New Haven, CT 06510

Department of Human Genetics
Genetic Consultation Service

Director:	Margretta R. Seashore, M.D.
Gen. Counselor:	Jodi Rucquoi, M.S. - Pediatrics
Phone:	203-785-2660
Gen. Counselor:	Miriam Schoenfeld DiMaio, M.S.W. - Prenatal Diagnosis
Phone:	203-785-2661
Services:	Biochemical Genetics, Clinical Genetics, Molecular Diagnosis, Cytogenetics, Genetic Counseling, Prenatal Diagnosis, Neurofibromatosis Clinic, Inborn Errors Clinic.
Outreach Sites:	Bridgeport, Danbury, Norwalk.

Norwalk Hospital
Maple Street
Norwalk, CT

Department of Pathology
Cytogenetics Laboratory

Director: Venkateswara Potluri, Ph.D.
Phone: 203-852-3423
Gen. Counselors: Lucinda L. Malin, M.S.
JoAnn Inserra, M.S.
Genetic Services
Phone: 203-852-3140/3359
Services: Cytogenetics, Genetic Counseling.

ME ME ME

State Genetics Program

Maine State Genetics Program
Maternal and Child Health
State House, Station 11
151 Capital Street
Augusta, ME 04333

Contact: Cheryl DiCarra
Phone: 207-289-3311
Services: Supports Genetic Services throughout the State, Coordination of Newborn Screening.

Eastern Maine Medical Center
89 State Street
Bangor, ME 04401

Department of Pediatrics
Genetics Program

Director: Laurent J. Beauregard, Ph.D.
Gen. Counselor: Mindy Rice, M.S.
Phone: 207-945-7354
Services: Clinical Genetics, Diagnostic Testing, Genetic Counseling, Prenatal Counseling, Cytogenetics, Molecular Genetics.
Outreach Sites: Calais, Presque Isle.

Neuromuscular Program

Director: Bob Gause, M.D.
Contact: Bonnie Deane
Phone: 207-945-7354

Center for Human Genetics
Firehouse Hill
Bar Harbor, ME 04609

Director: Melba Wilson, Ph.D.
Contact: Melba Wilson, Ph.D.
Phone: 207-288-5815
Services: Genetic Counseling.

Southern Maine Genetic Services
Foundation For Blood Research
P.O. Box 190
Scarborough, ME 04070-190

Director: Richard Doherty, M.D.
Contact: Deborah Adams
Phone: 207-883-4131
800-698-5551 (toll-free within Maine)
Gen. Counselors: Renee Laux, M.S.
Dale Lea, B.S.N.
Katherine Foss, M.S., R.N.
A. Merrill Henderson, M.S.

Services: Biochemical Genetics, Clinical Genetics, Diagnostic Testing, Genetic Counseling, Prenatal Diagnosis.

State Genetics Program

Massachusetts Genetics Program
Massachusetts Department of Public Health
150 Tremont Street, 2nd Floor
Boston, MA 02111

Contacts: Marsha T. Lanes, M.S., Director
Robin J.R. Blatt, M.P.H., Education Coordinator
Elizabeth Bingay, Congenital Anomaly Surveillance Coordinator
Phone: 617-727-5121
Services: Consumer Information and Referral, Health Care Provider Education, Teacher Training and Curriculum Development, Congenital Anomaly Surveillance, Technical Assistance in Genetics Education Materials and Projects, Grant Preparation and Implementation, Liaison to Newborn Screening, Genetics Education and Outreach to Underserved Populations.

Berkshire Medical Center
725 North Street
Pittsfield, MA 01201

The Genetics Program

Director:	Arthur Bloom, M.D.
Contact:	Debra Deres
Phone:	413-447-2403
Services:	Clinical Genetics, Cytogenetics, Genetic Counseling, MSAFP Screening Program.

Baystate Medical Center
759 Chestnut Street
Springfield, MA 01199

Cytogenetics Laboratory

Director:	Solveig M.V. Pflueger, M.D.
Gen. Counselors:	Tina Marini, M.S. Jan Warsing, M.S.
Contact:	Robert Gasparini, Ph. D.
Phone:	413-784-4363/5130
Services:	Clinical Genetics, Cytogenetics, Genetic Counseling, MSAFP Screening Program, Prenatal Diagnosis.

Boston City Hospital
818 Harrison Avenue
Boston, MA 02118

Boston Sickle Cell Center

Director:	Lillian McMahon, M.D.
Gen. Counselor:	Jan Warsing, M.S.
Phone:	617-534-5727
Services:	Clinical laboratory and counseling services for sickle cell anemia and other hemoglobinopathies.

Boston University Medical Center
80 East Concord Street
Boston, MA 02118

Center for Human Genetics

Director:	Aubrey Milunsky, MB.B.Ch., D. Sc., F.R.C.P., D.C.H.
Contact:	Doreen Martis
Phone:	617-638-7083
Services:	Biochemical Genetics, Clinical Genetics, Cytogenetics, DNA Analysis, Genetic Counseling, MSAFP Screening Program, Paternity Testing, Prenatal Diagnosis.

Brigham and Women's Hospital

75 Francis Street
Boston, MA 02115

Antenatal Diagnostic Center

Director: Louise Wilkins, M.D., Ph.D.
Assoc. Geneticist: Lewis B. Holmes, M.D.
Phone: 617-732-5445
Gen. Counselor: Janice M. Stryker, M.S.
Phone: 617-732-7771
Services: Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, MSAFP Screening Program, Prenatal Diagnosis.

Cytogenetics Laboratory

Director: Cynthia Morton, Ph.D.
Gen. Counselors: Janice Stryker, M.S.
Mary Francis Garber, M.S.
Marisa Ladoulis, M.S.
Phone: 617-732-7981
Services: Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, MSAFP Screening Program, Prenatal Diagnosis.

Teratogen Exposure Registry and Surveillance (TERAS)
Department of Pathology

Director: Frederick R. Bieber, Ph.D.
Phone: 617-732-6507
Services: Human Embryopathology, Fetal Pathology, Consultation Concerning Teratogen Exposed Human Pregnancies, Proper Study and Analysis of Autopsy Data, Referral of Human Fetal Material for Consultation and Diagnosis by Pathologists and Geneticists, Referral to Local Pathologists (part of the New England Regional Network for the Study of Teratogen Exposed Human Conceptuses).

Genetics Clinic

Director: Peter V. Tishler, M.D.
Contact: Peter V. Tishler, M.D.
Phone: 617-732-4838 (Clinic)
508-583-4500 x279 (Office)
Services: Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling and Treatment, Long Term Follow-up.

Children's Hospital

300 Longwood Avenue
Boston, MA 02115

Birth Defects Center

Director: Marilyn Haynie, M.D.
Contact: Judith Brewer, R.N., R.N.C.
Phone: 617-735-7037
Services: Coordinated Care of Multiply Disabled Children, Treatment, Long Term Follow - Up, Case Management Care.

Clinical Genetics

Director: Bruce Korf, M.D.
Gen. Counselors: Pam Hawley, M.S., Leanne Haskin-Leahy, M.S.
Phone: 617-735-6394
Services: Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, Development Evaluation, DNA Analysis, Biochemical Genetics.

Developmental Evaluation Center

Director: Allen Crocker, M.D.
Contact: Karen Morelli
Phone: 617-735-6509
Services: Diagnostic Study and Care Coordination of Children with Disability, Special Concern with Lipidoses and Mucopolysaccharidoses, Down Syndrome and Related Conditions.

Harvard Community Health Plan
185 Dartmouth Street
Boston, MA 02116

Genetics Department

Director: Susan Pauker, M.D.
Gen. Counselors: Martha MacMillin, M.S., Susan Mecsas-Faxon, M.S.
Phone: 617-859-5150
Services: Clinical Genetics, Genetic Counseling, MSAFP Screening, Referral for Cytogenetics.

Franciscan Children's Hospital
30 Warren Street
Brighton, MA 02135

National Birth Defects Center

Director: Murray Feingold, M.D.
Contact: Caroline Hobbs
Gen. Counselor: Karen Treat, M.S.
Phone: 617-787-5958
Services: Clinical Genetics, Diagnostic Clinical Evaluation and Testing, Genetic Counseling, Prenatal Counseling.

Massachusetts General Hospital
55 Fruit Street
Boston, MA 02144

Embryology Teratology Unit & Genetics Unit

Director: Lewis B. Holmes, M.D.
Contact: Neuza M.A. de Figueredo
Phone: 617-726-1742
Services: Clinical Genetics and Teratology, Diagnostic Clinical Evaluation and Testing, Cytogenetics, Prenatal and Genetic Counseling.

Amino Acid Disorders Laboratory

Director:	Vivian Shih, M.D.
Assoc. Director:	Harvey L. Levy, M.D.
Contact:	Kate Kirsch
Phone:	617-726-3884
Services:	Clinical Genetics, Cytogenetics, Diagnosis and Treatment of Inherited Metabolic Diseases, Genetic Counseling.

New England Medical Center, Inc.

750 Washington Street
Box 434
Boston, MA 02111

Center for Genetic Counseling and Birth Defects Evaluation

Director:	Mary Ampola, M.D.
Contact:	Kate Kirsch
Phone:	617-956-5454
Services:	Clinical Genetics, Cytogenetics, Genetic Counseling, Prenatal Counseling.

Prenatal Diagnostic Center, Inc.

80 Hayden Avenue
Lexington, MA 02173

Director:	Wayne A. Miller, M.D.
Gen. Counselors:	Barbara A. Thayer, M.S, Associate Director, Bonnie R. Braddock, M.S., Valerie Hastings, M.S., Kathryn Spitzer-Kim, M.S.
Phone:	617-862-1171
Services:	Prenatal Diagnosis, Genetic Counseling, Clinical Genetics, MSAFP Screening Program, Cytogenetics.

The Shriver Center for Mental Retardation, Inc.

200 Trapelo Road
Waltham, MA 02154

Division of Medical Genetics

Director:	Marvin Natowicz, M.D. Ph.D
Gen. Counselors:	Janet Rosenfield,M.S., Denise Lafayette, M.S.
Phone:	617-642-0170
Services:	Clinical Genetics, Cytogenetics, Referral for DNA Analysis, Genetic Counseling, MSAFP Screening Program, Prenatal Diagnosis.

Lysosomal Storage Disease Laboratory

Director:	Marvin Natowicz, M.D., Ph.D.
Assis. Director:	Elizabeth Prence, Ph.D.
Phone:	617-642-0175
Services:	This program provides clinical and laboratory services for the pre and post natal diagnosis of lysosomal storage diseases and certain other inherited metabolic diseases.

Tay-Sachs Prevention Program

Director: Marvin Natowicz, Ph.D., M.D.
Assis. Director: Elizabeth Prence, Ph.D.
Contact: Ruth Faucher, Elizabeth Williams
Phone: 617-642-0175
Services: Serum and leukocyte testing to identify carriers of Tay Sachs disease, Analysis of cultured amniotic fluid cells and chorionic villus tissue for the prenatal diagnosis of Tay Sachs disease, Counseling and community education.

State Laboratory Institute
305 South Street
Jamaica Plain, MA 02130

New England Regional Newborn Screening Program

Director: Marvin Mitchell, M.D.
Assis. Director: Harvey L. Levy, M.D.
Contact: Cecelia Walraven, Deborah Frederick
Phone: 617-522-3700 x157
Services: Newborn Screening, Follow-up Testing.

Sickle Cell Division

Director: Lillian McMahon, M.D.
Gen. Counselor: Emily Lazar, M.S.
Phone: 617-522-3700 x457
Services: Newborn Screening, Carrier Testing, Education, In-Service Training, Clinical Care Coordination, Hemoglobin Trait Counseling, Genetic Counseling.

University of Massachusetts Medical Center
55 Lake Avenue North
Worcester, MA 01605

Genetics Clinic

Director: Philip L. Townes, M.D., Ph.D.
Gen. Counselor: Mary L. Simmons, M.S.
Phone: 617-856-6447
Services: Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, Prenatal Diagnosis.

NH NH NH

State Genetics Program

Division of Public Health
Bureau of Special Medical Services
Health and Welfare Building
6 Hazen Drive
Concord, NH 03301

Genetic Services Program
Bureau Chief: Jane Hybsch
Program Coordinators: Susan Z. Berg, M.S. - Genetics; Susan Moore, R.N. - Newborn Screening
Phone: 603-271-4596
Services: Maintains a regional network of genetic clinics; Provides complete diagnostic evaluation; Supportive and Informational Counseling; Information regarding identification of carriers of recessive genetic disorders and certain chromosome disorders.
Outreach Sites: Berlin/Littleton; Concord; Dover/Rochester; Keene/Peterborough; Laconia; Manchester; Nashua.

Dartmouth-Hitchcock Medical Center
Department of Maternal and Child Health
Hanover, NH 03756

Clinical Genetics and Child Development Center

Director:	John B. Moeschler, M.D. (Clinical Genetics)
Assoc. Director:	Carl Cooley, M.D. (Child Development)
Gen.Counselors:	Melanie McDermet, M.S. - Clinical Genetics; Eileen Rawnsley, R.N., B.S.N. - Prenatal Diagnosis
Phone:	603-646-8453
Services:	Clinical Genetics and Dysmorphology, Clinical Teratology, Fetal Pathology, Diagnostic Testing, Genetic Counseling, Prenatal Diagnosis, Developmental Evaluation, Cytogenetics, Down Syndrome Clinic, Molecular Genetics Diagnostic Laboratory.
Outreach Sites:	Genetic Services Program through Public Health.

RI RI RI

State Genetics Program

Division of Family Health
Rhode Island Department of Health
Canon Building
3 Capitol Hill
Providence, RI 02908

Contact: Amy Zimmerman, M.S.
Phone: 401-277-2312
Services: Materials Development; Information and Referral; Coordination of Newborn Screening.

Rhode Island Hospital
Providence, RI 02903

Genetic Counseling Center

Director:	Dianne Abuelo, M.D.
Contact:	Dianne Abuelo, M.D.
Phone:	401-277-8361
Services:	Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, Prenatal Diagnosis.

Women's and Infants Hospital
101 Dudley Street
Provdence, RI 02905

Prenatal AFP & Cytogenetics Laboratories

Director:	Jacob Canick, Ph.D.
Contact:	Anne Richardson, M.S. (Cytogenetics) Diane Panizza, Marea Tumber (Prenatal AFP)
Phone:	401-831-1622
Services:	AFP Screening Program, Cytogenetics.

Prenatal Diagnostic Center

Contact:	Devereux Saller, Jr., M.D.
Gen. Counselors:	Debra Lochner Doyle, M.S. Jacquelyn V. Dailey, M.S. Mary-Jo Tout, M.S.
Phone:	401-454-5455
Services:	Prenatal Diagnosis, Genetic Counseling.

VT VT VT

State Genetics Program

Division of Public Health
Vermont Department of Health
1193 North Avenue
P.O. Box 70
Burlington, VT 05402

Contact: Ellen Thompson, R.D., M.S.
Phone: 802-863-7606
Services: Coordinates statewide Genetic Services, including Newborn Screening; Provides funding for the Regional Genetic Center.

Vermont Regional Genetics Center
1 Mill Street, Suite 3-1
Burlington, VT 05401

Director:	Alan Guttmacher, M.D.
Gen. Counselor:	Barbara West, M.S.
Phone:	802-658-4310
Services:	Biochemical Genetics, Clinical Genetics, Cytogenetics, Genetic Counseling, Prenatal Diagnosis, Pregnancy Risk Information Service.
Outreach Sites:	Bennington, Brattleboro, Middlebury, Newport, Rutland, St. Johnsbury, Barre, Plattsburg, New York.

Genes & Human Behavior

A New Era?

a conference for scientists and journalists
organized by The Genetic Screening Study Group

Harvard Medical School
Saturday, October 26, 1991

Medical Education Center Amphitheater
260 Longwood Avenue, Boston

8:30 Registration

9:00 Introductory Remarks

9:05 Perspectives on Human Behavioral Genetics
Richard Lewontin, Harvard University
Sandra Scarr, University of Virginia
Miron Baron, Columbia University College of Physicians and Surgeons

10:30 Coffee Break

11:00 Media Coverage of Human Behavioral Genetics
Robert Bazell, NBC-TV News
Richard Saltus, The Boston Globe
Constance Holden, Science Magazine

12:30 Lunch

1:30 Genetics & Mental Illness
Kenneth Kidd, Yale University
Marvin Natowicz, The Shriver Center for Mental Retardation
Alfie Kohn, Author of "The Brighter Side of Human Nature: Altruism and Empathy in Everyday Life"

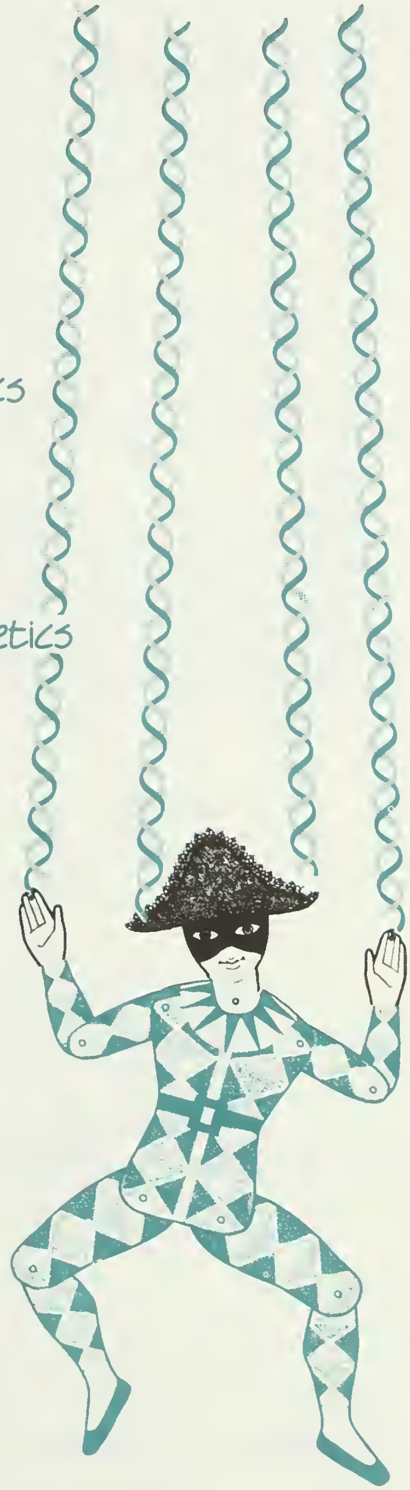
2:30 Coffee Break

3:00 Genetics & Alcoholism
Donald Goodwin, University of Kansas Medical Center
Kaye Fillmore, University of California, San Francisco
Stanton Peele, Addiction Theorist and Co-author of "The Truth about Addiction and Recovery"

4:00 Genes & Gender
Anne Fausto-Sterling, Brown University

4:45 Summary Remarks
Jon Beckwith, Harvard Medical School

5:00 Closure



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Registration Information:
Charge to Attendees: $45.00 Fee includes materials for Conference and lunch. Scholarships available on request. Send name, address and check payable to **"Science & Journalism Conference"** to:

Science & Journalism Conference
c/o Professor Jon Beckwith
Harvard Medical School
Boston, MA 02115

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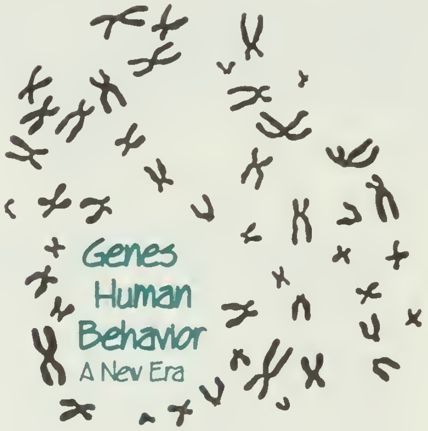
Genes & Human Behavior " make great press. The nation's leading newspapers often choose to feature studies on the inheritance of behavioral conditions with front page headlines. For instance, last year's report of a gene for alcoholism received extensive publicity. Subsequent studies that raised question about the initial report were relegated to the back pages. The apparent discovery of a gene for manic depression attracted even more attention. The later news that the conclusions of the study had been retracted received considerably less coverage. These and other examples raise questions as to how new scientific claims in the field of human behavioral genetics are to be evaluated by the media.

Despite these recent problems, researchers in behavioral genetics now have available to them scientific tools that can revolutionize the field. Dramatic advances in gene mapping techniques permit the determination of the location of genes for various human behavioral conditions. They may also help scientists to distinguish between those conditions that have a genetic component and those that are caused mainly by environmental factors. The existence of these new techniques holds the promise of making human behavioral genetics a much more precise science. However, without strict criteria for the use of these new approaches by researchers, the mistakes of the past may be repeated.

Since the founding of genetics, the field of "Genes & Human Behavior" has been a controversial one. In the past, unsubstantiated assertions about genetically inherited behavior resulted in discrimination against individuals and groups and in the misdirection of social policy. How we, as individuals or as a society, deal with people who have various mental disorders may be influenced by scientific studies in this field and their interpretation. Therefore, it is important that the science of behavioral genetics be done and presented to the public in the most careful manner.

The purpose of this Conference is to explore these issues. We will begin with a panel of speakers who will discuss behavioral genetics from identical twin studies to the latest DNA technologies. The panel will include scientists with different points of view on the benefits and limitations of this research. The second panel will consist of journalists who are involved in covering the field. Both the pressures on journalists and their interactions with scientists will be presented. The next three sessions will explore various aspects of the transfer of scientific research to the public domain in the fields of mental illness, alcoholism and sex differences. A final talk will summarize the major points of the Conference.



Science & Journalism III

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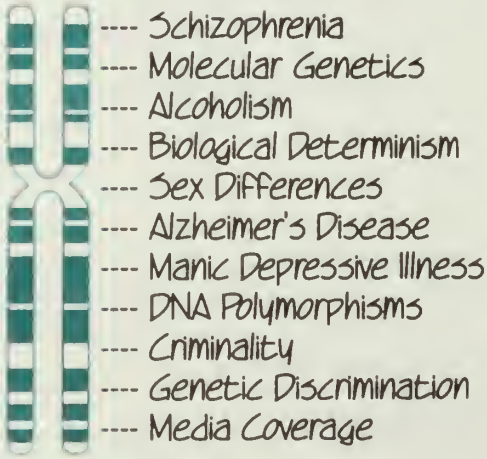
A New Era ?

a conference at the

Harvard Medical School

Saturday October 26, 1991



The Genetic Resource
Reader Survey & Subscriber Information

Over the past decade **The Genetic Resource** has provided you with current information on new developments in genetics and its applications to different clinical specialties. The 1990's is sure to bring about new discoveries and rapid changes in the application of genetic testing in medical practice. In our last issue we asked you whether you would pay a subscription fee to continue to receive this publication. While many respondents indicated that a subscription fee would be possible, we have decided not to exercise that option at this time. Instead we are encouraging **donations** to help to offset the costs associated with the production and mailing. All contributions will be acknowledged in the upcoming issue. As you know, we strive to bring you the latest information in genetics. In order to continue this tradition, please complete this Reader Survey and the accompanying Subscriber Information. And please consider making a donation. Return immediately to the address below. Thank you!

① Given the current state of the art, what do you think about incorporating biochemical markers such as unconjugated estriol(UE3) and human chorionic gonadotropin (hCG) into existing maternal serum alpha-fetoprotein (AFP) screening programs in order to enhance the detection of fetal Down syndrome?

☐ It's a good idea
☐ It's not a good idea
☐ Undecided
Comments: ______________________
____

② Given the current state of the art, what do you think about population-based carrier screening for cystic fibrosis?

☐ It's a good idea
☐ It's not a good idea (If not, why?)
☐ Undecided
Comments: ______________________
____

③ Given the rapid pace of development in the field of human genetics, do you feel sufficiently able to remain current?

☐ Yes
☐ No
☐ Undecided
Comments: ______________________
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④ What is your impression of the new format of The Genetic Resource?

☐ Positive
☐ Negative
☐ Undecided
Comments: ______________________
____

⑤ Would you be interested in reading about the Human Genome Project and the accompanying ethical, legal, and social implications?

☐ Yes
☐ No
☐ Undecided
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⑥ What other topics would you like to see covered in future issues of The Genetic Resource?

Comments: ______________________
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